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59-23-4 OR  9000-01-5)/rn
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113852-37-2 OR 161363-19-5 OR 123994-68-3 OR 59-23-4 OR 9000-01-5)/RN

=> s (9002-89-5 OR 9004-34-6 OR 9005-25-8 OR 9012-36-6 OR 24980-41-4 OR 25248-42-4 OR 26023-30-3 OR 26063-00-3 OR 26100-51-6 OR 26744-04-7 OR 26913-47-3 OR 28158-18-1 OR 28803-92-1 OR 34346-01-5 OR 90409-78-2 OR 121065-55-2 OR 718636-43-2)/rn

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             0 121065-55-2D
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              26744-04-7 OR 26913-47-3 OR 28158-18-1 OR 28803-92-1 OR 34346-01-
              5 OR 90409-78-2 OR 121065-55-2 OR 718636-43-2)/RN

=> d his

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L5   ANSWER 1 OF 1  HCAPLUS  COPYRIGHT 2007 ACS on STN
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DOCUMENT NUMBER:          141:185078
TITLE:                    Novel antiherpes drug combinations of Herpes simplex
                          virus thymidine kinase inhibitors and antiherpes
                          substances
INVENTOR(S):              Wright, George E.
PATENT ASSIGNEE(S):       University of Massachusetts, USA
SOURCE:                   PCT Int. Appl., 22 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE       APPLICATION NO.          DATE
     ---------------      ----   --------   ---------------------    --------
     WO 2004069168         A2    20040819   WO 2004-US2427           20040129
     WO 2004069168         A3    20050915
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI
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MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2514334	A1	20040819	CA 2004-2514334	20040129
US 2004259832	A1	20041223	US 2004-767019	20040129 <--
EP 1594507	A2	20051116	EP 2004-706459	20040129

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK

PRIORITY APPLN. INFO.: US 2003-443519P P 20030129
WO 2004-US2427 W 20040129

AB Composition and methods are disclosed that include a synergistic combination of an inhibitor of Herpes simplex virus thymidine kinase, and an antiherpes substance. The effect of combination of 2-phenylamino-9-(4-hydroxybutyl)-6-oxopurine and foscarnet against HSV2 encephalitis in mice was examined

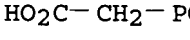
IT 9002-06-6, Thymidine kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Herpes simplex virus; antiherpes drug combinations of Herpes simplex virus thymidine kinase inhibitors and antiherpes substances)

RN 9002-06-6 HCAPLUS
CN Kinase (phosphorylating), thymidine (CA INDEX NAME)

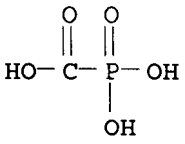
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT 4408-78-0 4428-95-9, Foscarnet 59277-89-3, Acyclovir 66341-16-0, Acyclovir monophosphate 82410-32-0, Ganciclovir 86761-39-9 104227-87-4, Famciclovir 106941-25-7, PMEA 113852-37-2, Cidofovir 161363-19-5
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiherpes drug combinations of Herpes simplex virus thymidine kinase inhibitors and antiherpes substances)

RN 4408-78-0 HCAPLUS
CN Acetic acid, 2-phosphono- (CA INDEX NAME)



RN 4428-95-9 HCAPLUS
CN Phosphinecarboxylic acid, 1,1-dihydroxy-, 1-oxide (CA INDEX NAME)



RN 59277-89-3 HCAPLUS
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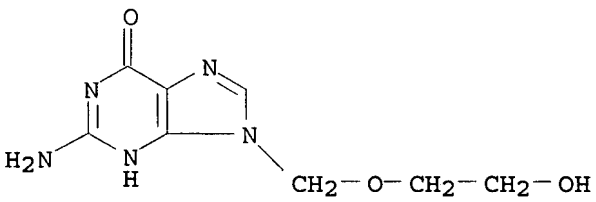
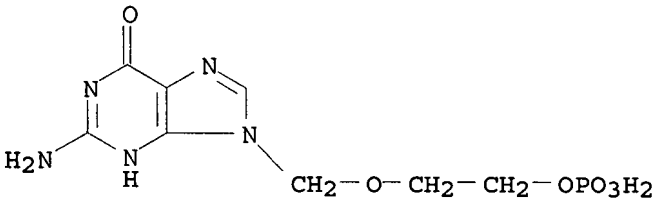
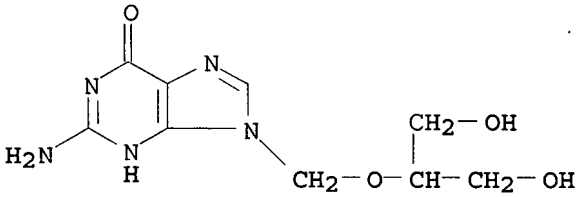


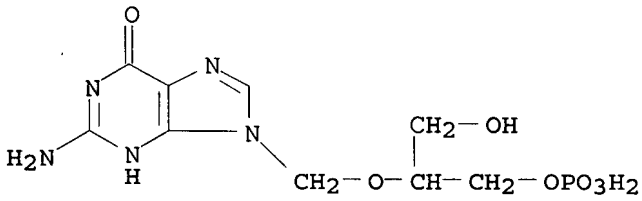
RN 66341-16-0 HCAPLUS
CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[[2-(phosphonooxy)ethoxy]methyl]- (CA INDEX NAME)



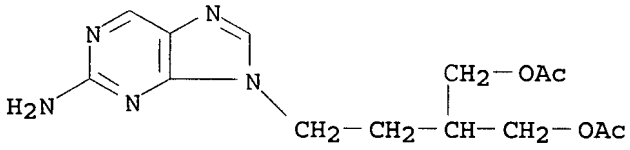
RN 82410-32-0 HCAPLUS
CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]- (CA INDEX NAME)



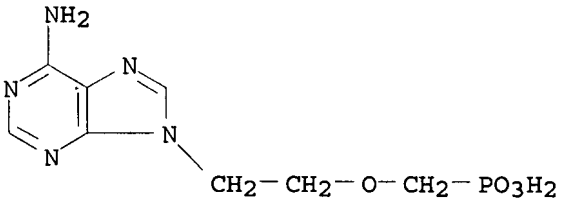
RN 86761-39-9 HCAPLUS
CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[[1-(hydroxymethyl)-2-(phosphonooxy)ethoxy]methyl]- (CA INDEX NAME)



RN 104227-87-4 HCAPLUS
CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-, 1,3-diacetate (CA INDEX NAME)

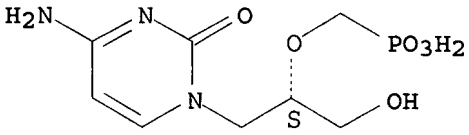


RN 106941-25-7 HCAPLUS
CN Phosphonic acid, P-[[2-(6-amino-9H-purin-9-yl)ethoxy]methyl]- (CA INDEX NAME)

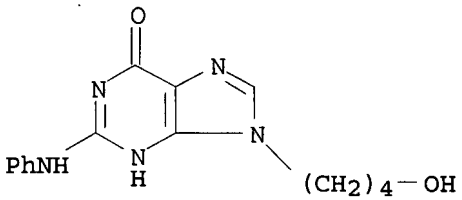


RN 113852-37-2 HCAPLUS
CN Phosphonic acid, P-[[(1S)-2-(4-amino-2-oxo-1(2H)-pyrimidinyl)-1-(hydroxymethyl)ethoxy]methyl]- (CA INDEX NAME)

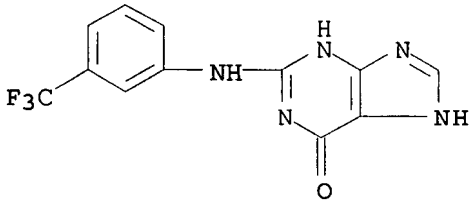
Absolute stereochemistry.



RN 161363-19-5 HCAPLUS
CN 6H-Purin-6-one, 1,9-dihydro-9-(4-hydroxybutyl)-2-(phenylamino)- (9CI) (CA INDEX NAME)



IT 123994-68-3
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiherpes drug combinations of Herpes simplex virus thymidine kinase inhibitors and antiherpes substances)
RN 123994-68-3 HCAPLUS
CN 6H-Purin-6-one, 1,7-dihydro-2-[[3-(trifluoromethyl)phenyl]amino]- (9CI) (CA INDEX NAME)

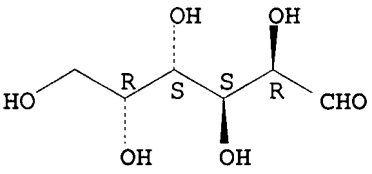


IT 59-23-4, Galactose, biological studies 9000-01-5, Gum arabic 9002-89-5, Polyvinylalcohol 9004-34-6, Cellulose, biological studies 9005-25-8, Starch, biological studies 9012-36-6, Agarose 24980-41-4,

Polycaprolactone 25248-42-4, Polycaprolactone 26023-30-3
, Poly[oxy(1-methyl-2-oxo-1,2-ethanediyl)] 26063-00-3,
Polyhydroxybutyrate 26100-51-6, Lactic acid homopolymer
26744-04-7 26913-47-3, Poly[oxy(1,10-dioxo-1,10-
decanediyl)] 28158-18-1 28803-92-1 34346-01-5
, Lactic acid-glycolic acid copolymer 90409-78-2,
1,3-Bis(carboxyphenoxypropane)-sebacic acid copolymer 121065-55-2
718636-43-2
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiherpes drug combinations of Herpes simplex virus thymidine kinase
inhibitors and antiherpes substances and carriers)

RN 59-23-4 HCAPLUS
CN D-Galactose (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

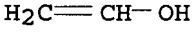


RN 9000-01-5 HCAPLUS
CN Gum arabic (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 9002-89-5 HCAPLUS
CN Ethenol, homopolymer (CA INDEX NAME)

CM 1

CRN 557-75-5
CMF C2 H4 O



RN 9004-34-6 HCAPLUS
CN Cellulose (CA INDEX NAME)

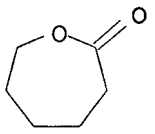
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 9005-25-8 HCAPLUS
CN Starch (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 9012-36-6 HCAPLUS
CN Agarose (CA INDEX NAME)

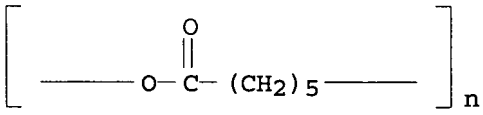
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 24980-41-4 HCAPLUS
CN 2-Oxepanone, homopolymer (CA INDEX NAME)

CM 1

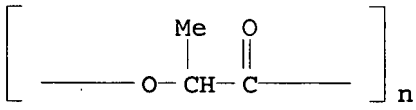
CRN 502-44-3
CMF C6 H10 O2



RN 25248-42-4 HCAPLUS
CN Poly[oxy(1-oxo-1,6-hexanediyl)] (CA INDEX NAME)



RN 26023-30-3 HCAPLUS
CN Poly[oxy(1-methyl-2-oxo-1,2-ethanediyl)] (CA INDEX NAME)



RN 26063-00-3 HCAPLUS
CN Butanoic acid, 3-hydroxy-, homopolymer (CA INDEX NAME)

CM 1

CRN 300-85-6
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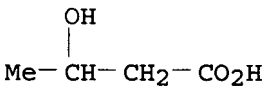

RN 26100-51-6 HCAPLUS
CN Propanoic acid, 2-hydroxy-, homopolymer (CA INDEX NAME)

CM 1

CRN 50-21-5
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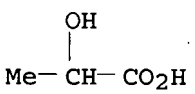
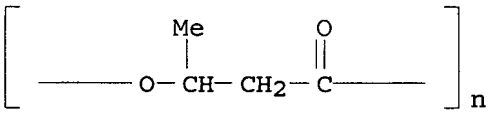
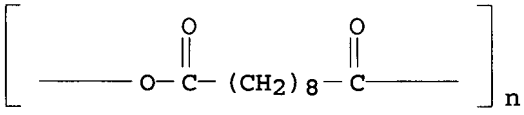


RN 26744-04-7 HCAPLUS
CN Poly[oxy(1-methyl-3-oxo-1,3-propanediyl)] (CA INDEX NAME)



RN 26913-47-3 HCAPLUS
CN Poly[oxy(1,10-dioxo-1,10-decanediyl)] (CA INDEX NAME)



RN 28158-18-1 HCAPLUS
CN Hexanoic acid, 6-hydroxy-, homopolymer (CA INDEX NAME)

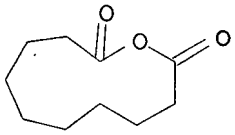
CM 1

CRN 1191-25-9
CMF C6 H12 O3

RN 28803-92-1 HCAPLUS
CN Oxacycloundecane-2,11-dione, homopolymer (CA INDEX NAME)

CM 1

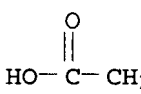
CRN 2561-88-8
CMF C10 H16 O3



RN 34346-01-5 HCAPLUS
CN Propanoic acid, 2-hydroxy-, polymer with 2-hydroxyacetic acid (CA INDEX NAME)

CM 1

CRN 79-14-1
CMF C2 H4 O3



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CRN 50-21-5
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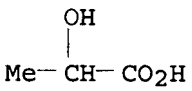
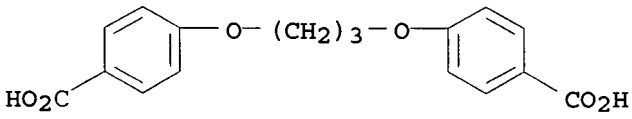


RN 90409-78-2 HCAPLUS
CN Decanedioic acid, polymer with 4,4'-[1,3-propanediylbis(oxy)]bis[benzoic acid] (CA INDEX NAME)

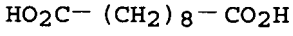
CM 1

CRN 3753-81-9
CMF C17 H16 O6



CM 2

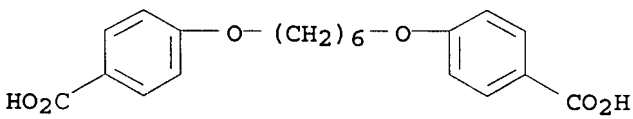
CRN 111-20-6
CMF C10 H18 O4



RN 121065-55-2 HCAPLUS
CN Decanedioic acid, polymer with 4,4'-[1,6-hexanediylbis(oxy)]bis[benzoic acid] (CA INDEX NAME)

CM 1

CRN 74774-53-1
CMF C20 H22 O6



CM 2

CRN 111-20-6

10767019>05/05/2007

CMF C10 H18 O4

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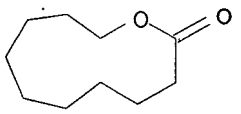
RN 718636-43-2 HCAPLUS
CN Oxacycloundecan-2-one, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 5579-79-3
CMF C10 H18 O2



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=> fil stng
COST IN U.S. DOLLARS

	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	13.07	17.70

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-0.78	-0.78

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FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Apr 27, 2007 (20070427/UP).

=> d his

(FILE 'HOME' ENTERED AT 15:58:27 ON 02 MAY 2007)

FILE 'HCAPLUS' ENTERED AT 15:58:36 ON 02 MAY 2007
E US20040259832/PN 25
L1 1 S E3

FILE 'STNGUIDE' ENTERED AT 15:59:26 ON 02 MAY 2007

FILE 'HCAPLUS' ENTERED AT 16:02:09 ON 02 MAY 2007
L2 43567 S (9002-06-6 OR 4408-78-0 OR 4428-95-9 OR 59277-89-3 OR 66341-
L3 237600 S (9002-89-5 OR 9004-34-6 OR 9005-25-8 OR 9012-36-6 OR 24980-4
L4 276194 S L2 OR L3
L5 1 S L4 AND L1

FILE 'STNGUIDE' ENTERED AT 16:03:41 ON 02 MAY 2007

=> fil hcaplus

10767019>05/05/2007

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.42	18.12

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-0.78

FILE 'HCAPLUS' ENTERED AT 16:07:58 ON 02 MAY 2007
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FILE COVERS 1907 - 2 May 2007 VOL 146 ISS 19
FILE LAST UPDATED: 1 May 2007 (20070501/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate
substance identification.

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              )/RN

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        278618 "INFECTION"
         80491 "INFECTIONS"
        317344 "INFECTION"
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        255359 "SKIN"
         10347 "SKINS"
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        950108 "DISEASE"
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L7         2471 L6 AND (HERPES OR "HERPES" OR "INFECTION" (L) "HERPES" OR "SKIN,
                DISEASE" (L) "HERPES")

=> d l7 ibib abs hitstr

L7   ANSWER 1 OF 2471  HCAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:        2007:268504  HCAPLUS <<LOGINID::20070502>>
DOCUMENT NUMBER:         146:386676
TITLE:                   Effects of bicistronic lentiviral vector-mediated
                         herpes simplex virus thymidine
                         kinase/ganciclovir system on human lens epithelial
                         cells
AUTHOR(S):               Yang, Jin; Liu, Tian Jin; Lu, Yi
CORPORATE SOURCE:        Department of Ophthalmology, Eye and ENT Hospital,
                         Fudan University, Shanghai, Peop. Rep. China
SOURCE:                  Current Eye Research (2007), 32(1), 33-42
                         CODEN: CEYRDM; ISSN: 0271-3683
PUBLISHER:               Taylor & Francis, Inc.
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   Posterior capsule opacification (PCO) is the most common complication
     after phacoemulsification cataract surgery.  Hyperplasia of the lens
     epithelial cell after phacoemulsification is thought to be an important
     feature contributing to PCO.  In this study, we investigated the
     feasibility of killing the human lens epithelial cells (HLECs) by
     lentivirus-mediated herpes simplex virus thymidine kinase
     (HSV-tk) gene/ganciclovir (GCV) in HLECs and studied the bystander effect.
     HLECs were infected with lentiviral vectors coexpressing HSV-tk and
     enhanced green fluorescent protein (EGFP) or expressing EGFP alone and
     treated with ganciclovir.  Infection efficiency was assessed by
     fluorescence microscopy, fluorescence-activated cell sorting, and reverse
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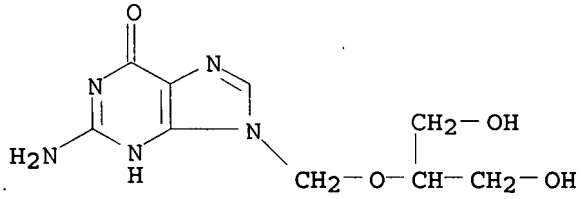
transcription PCR. The cytotoxicity of the HSV-tk/GCV suicide gene therapy system was assessed by DNA ladder and electron microscopy. The time effect and bystander effect of HLEC growth inhibition were evaluated with cell proliferation assay. Lentiviral vector-mediated stable integration and efficient expression of HSV-tk in HLECs, with infection efficiency exceeding 95% GCV at concns. of 15.apprx.25 μg/mL, significantly induced apoptosis or necrosis of infected HLECs. GCV also killed normal cells mixed with HSV-tk infected cells. The bystander effect markedly increased the cytotoxicity of the HSV-tk/GCV system. Our results suggest that bicistronic lentiviral vectors can efficiently integrate several genes into HLECs and may be a gene therapy platform. Lentivirus-mediated suicide gene therapy might be a feasible treatment strategy to prevent capsule opacification.

IT 82410-32-0, Ganciclovir
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(bicistronic lentiviral vector-mediated herpes simplex virus thymidine kinase/ganciclovir system exhibit higher cytotoxicity levels suggest that it can efficiently integrate several genes in human lens epithelial cells)

RN 82410-32-0 HCAPLUS
CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]- (CA INDEX NAME)



REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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=> s acyclovir ?phosphate?
         3855 ACYCLOVIR
       841237 ?PHOSPHATE?
L8        113 ACYCLOVIR ?PHOSPHATE?
              (ACYCLOVIR(W)?PHOSPHATE?)

=> s l8 and l7
L9         40 L8 AND L7

=> d l9 ibib abs hitstr

L9   ANSWER 1 OF 40  HCAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:        2007:150707  HCAPLUS <<LOGINID::20070502>>
DOCUMENT NUMBER:         146:198656
TITLE:                   Methods for treating or preventing reactivation of a
                         latent herpesvirus infection
INVENTOR(S):             Schaffer, Priscilla; Bringhurst, Ryan
PATENT ASSIGNEE(S):      Beth Israel Deaconess Medical Center, USA
SOURCE:                  PCT Int. Appl., 83pp.
                         CODEN: PIXXD2
DOCUMENT TYPE:           Patent
LANGUAGE:                English
FAMILY ACC. NUM. COUNT:  1
PATENT INFORMATION:
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PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007016450	A2	20070208	WO 2006-US29663	20060731

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2005-703835P P 20050729

AB The invention is directed to methods and compns. for treating or preventing reactivation of a latent herpesvirus infection and the associated complications and outcomes. The methods involve administering a composition comprising glutamine, or a derivative, conjugate, or analog thereof.

IT 59277-89-3, Acyclovir 66341-16-0, Acyclovir monophosphate 82410-32-0, Ganciclovir 86761-39-9 104227-87-4, Famciclovir 106941-25-7, PMEA 113852-37-2, Cidofovir
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods for treating or preventing reactivation of a latent herpesvirus infection using glutamine and its analogs in combination with other agents)

RN 59277-89-3 HCAPLUS

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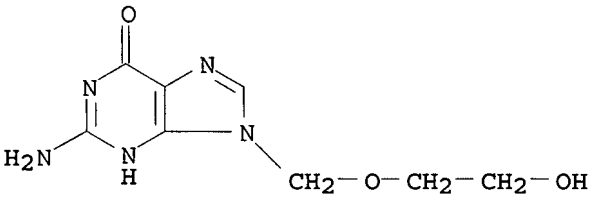

RN 66341-16-0 HCAPLUS

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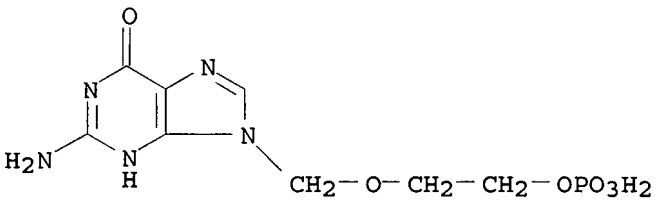

RN 82410-32-0 HCAPLUS

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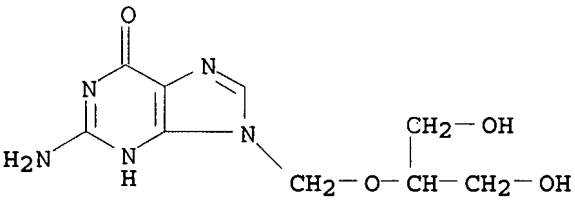

RN 86761-39-9 HCAPLUS
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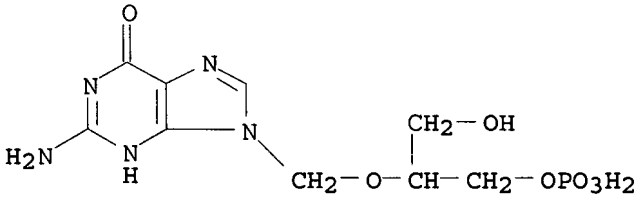
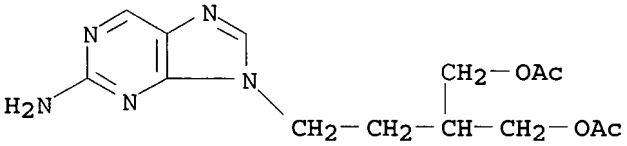
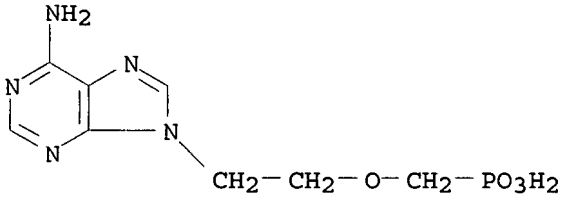


RN 104227-87-4 HCAPLUS
CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-, 1,3-diacetate (CA INDEX NAME)

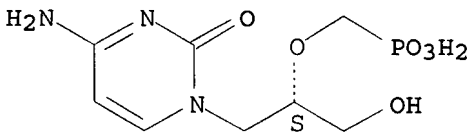


RN 106941-25-7 HCAPLUS
CN Phosphonic acid, P-[[2-(6-amino-9H-purin-9-yl)ethoxy]methyl]- (CA INDEX NAME)



RN 113852-37-2 HCAPLUS
CN Phosphonic acid, P-[[(1S)-2-(4-amino-2-oxo-1(2H)-pyrimidinyl)-1-(hydroxymethyl)ethoxy]methyl]- (CA INDEX NAME)

Absolute stereochemistry.



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     (FILE 'HOME' ENTERED AT 15:58:27 ON 02 MAY 2007)

     FILE 'HCAPLUS' ENTERED AT 15:58:36 ON 02 MAY 2007
                E US20040259832/PN 25
L1              1 S E3

     FILE 'STNGUIDE' ENTERED AT 15:59:26 ON 02 MAY 2007

     FILE 'HCAPLUS' ENTERED AT 16:02:09 ON 02 MAY 2007
L2          43567 S (9002-06-6 OR 4408-78-0 OR 4428-95-9 OR 59277-89-3 OR  66341-
L3         237600 S (9002-89-5 OR  9004-34-6 OR 9005-25-8 OR 9012-36-6 OR 24980-4
L4         276194 S L2 OR L3
L5              1 S L4 AND L1

     FILE 'STNGUIDE' ENTERED AT 16:03:41 ON 02 MAY 2007

     FILE 'HCAPLUS' ENTERED AT 16:07:58 ON 02 MAY 2007
L6           6746 S  (59277-89-3 OR 66341-16-0 OR 82410-32-0 OR 86761-39-9 OR 104
                E HERPES+ALL/CT
L7           2471 S L6 AND (HERPES OR "HERPES" OR "INFECTION" (L) "HERPES" OR "SK
L8            113 S ACYCLOVIR ?PHOSPHATE?
L9             40 S L8 AND L7

=> S L9 AND 1800<=PY<=2003
      23932189 1800<=PY<=2003
L10           38 L9 AND 1800<=PY<=2003

=> d l10 ibib abs hitstr

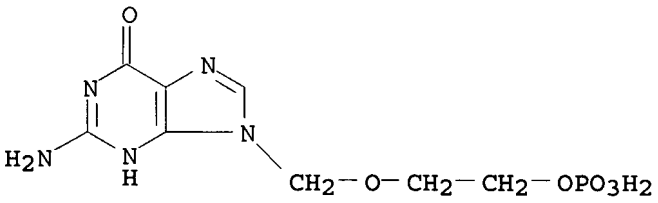
L10  ANSWER 1 OF 38  HCAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:         2002:153908  HCAPLUS <<LOGINID::20070502>>
DOCUMENT NUMBER:          137:338
TITLE:                    Antiviral activity of cyclosaligenyl prodrugs of
                          acyclovir, carbovir, and abacavir
AUTHOR(S):                Balzarini, Jan; Haller-Meier, Friederike; De Clercq,
                          Erik; Meier, Chris
CORPORATE SOURCE:         Rega Institute for Medical Research, KU Leuven,
                          Louvain, Belg.
SOURCE:                   Antiviral Chemistry & Chemotherapy (2001),
                          12(5), 301-306
                          CODEN: ACCHEH; ISSN: 0956-3202
PUBLISHER:                International Medical Press
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB   The cyclosaligenyl (cycloSal) derivs. of the monophosphates of 3 acyclic
     or carbocyclic guanosine analogs, for example, acyclovir (ACV), carbovir
     (CBV), and abacavir (ABC), were investigated for their activity against
     retrovirus (HIV, Moloney sarcoma virus) and herpes simplex virus
     (HSV) activity in cell culture.  The extent of the antiviral potency of
     the prodrugs depended on the nature of the nucleoside, the substituent on
     the cycloSal moiety and the virus investigated.  Most notably, and unlike
```

the parent compound ACV, cycloSal-ACV monophosphate (MP) prodrugs retained pronounced activity against ACV-resistant (thymidine kinase-deficient) HSV-1 and also gained anti-HIV activity. While the cycloSal-CBVMP prodrugs did not show enhanced activity compared with the parent compound CBV, the cycloSal-ABCMP prodrugs afforded markedly increased potency against both HSV and HIV. The authors' data indicate that the cycloSal prodrug approach can be useful to deliver directly the MP derivs. of nucleoside analogs into the intact, virus-infected cells, thus improving and extending the antiviral potency and spectrum of the drugs against retro- and herpesvirus strains.

IT 66341-16-0, Acyclovir monophosphate
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cyclosaligenyl prodrugs; antiviral activity of cyclosaligenyl prodrugs of acyclovir, carbovir, and abacavir)

RN 66341-16-0 HCAPLUS

CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[[2-(phosphonooxy)ethoxy]methyl]- (CA INDEX NAME)



REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d l10 ibib abs hitstr 2-10

L10 ANSWER 2 OF 38 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2001:580763 HCAPLUS <<LOGINID::20070502>>

DOCUMENT NUMBER: 135:327001

TITLE: The potency of acyclovir can be markedly different in different cell types

AUTHOR(S): Brandi, Giorgio; Schiavano, Giuditta F.; Balestra, Emanuela; Tavazzi, Barbara; Perno, Carlo-Federico; Magnani, Mauro

CORPORATE SOURCE: Institute of Toxicologic Hygienic and Environmental Science, "G. Fornaini" University of Urbino, Urbino, Italy

SOURCE: Life Sciences (2001), 69(11), 1285-1290
CODEN: LIFSAK; ISSN: 0024-3205

PUBLISHER: Elsevier Science Inc.

DOCUMENT TYPE: Journal

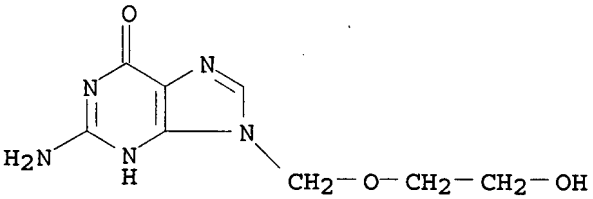
LANGUAGE: English

AB Acyclovir is an acyclic guanine analog with a considerable activity against herpes simplex viruses. We studied the antiherpetic activity of acyclovir in macrophages and fibroblast cell lines. Utilizing a plaque reduction assay we found that acyclovir potently inhibited the HSV-1 replication in macrophages (EC50 = 0.0025 μM) compared to Vero (EC50 = 8.5 μM) and MRC-5 (EC50 = 3.3 μM) cells. The cytotoxicity of acyclovir was not detected at concns. ≤ 20 μM, thus the selective index in macrophages was > 8000. This marked difference in antiherpetic activity between macrophages and fibroblasts was not observed with Foscarnet and PMEA. We suggest that this potent antiviral effect of acyclovir is mainly due to a proficient phosphorylation of the drug and/or

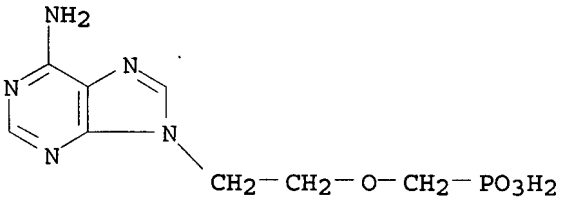
a favorable dGTP/acyclovir triphosphate ratio in macrophage cells.

IT 59277-89-3, Acyclovir 106941-25-7, PMEA
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(potency of acyclovir can be markedly different in different cell types)

RN 59277-89-3 HCAPLUS
CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]- (CA INDEX NAME)



RN 106941-25-7 HCAPLUS
CN Phosphonic acid, P-[[2-(6-amino-9H-purin-9-yl)ethoxy]methyl]- (CA INDEX NAME)



REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 3 OF 38 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:446743 HCAPLUS <<LOGINID::20070502>>
DOCUMENT NUMBER: 133:171805
TITLE: Antiviral activities of oral 1-O-hexadecylpropanediol-3-phosphoacyclovir and acyclovir in woodchucks with chronic woodchuck hepatitis virus infection
AUTHOR(S): Hostetler, Karl Y.; Beadle, James R.; Hornbuckle, William E.; Bellezza, Christine A.; Tochkov, Ilia A.; Cote, Paul J.; Gerin, John L.; Korba, Brent E.; Tennant, Bud C.
CORPORATE SOURCE: Department of Medicine, University of California, San Diego, La Jolla, CA, 92093-0676, USA
SOURCE: Antimicrobial Agents and Chemotherapy (2000), 44(7), 1964-1969
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

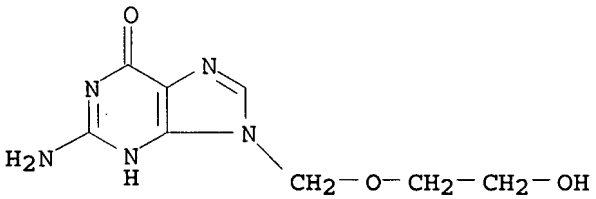
AB Acyclovir triphosphate is a potent inhibitor of hepatitis B virus DNA polymerase, but acyclovir treatment provides no benefit in patients with hepatitis B virus infection. This is due in part to the fact that hepatitis B virus, unlike herpes

simplex virus, does not code for a viral thymidine kinase which catalyzes the initial phosphorylation of acyclovir. We synthesized 1-O-octadecyl-sn-glycero-3-phospho (3-P)-acyclovir and found that it was highly active in reducing hepatitis B virus replication in 2.2.15 cells, while acyclovir was inactive. The greater antiviral activity of 1-O-octadecyl-sn-glycero-3-P-acyclovir appeared to be due to liver cell metabolism of the compound to acyclovir monophosphate. However, a closely related compound without a hydroxyl group at the sn-2 position of glycerol, 1-O-hexadecylpropanediol-3-P-acyclovir, was more active and selective in 2.2.15 cells in vitro. In this study, we treated woodchucks chronically infected with woodchuck hepatitis virus with increasing oral doses of 1-O-hexadecylpropanediol-3-P-acyclovir and assessed the response to therapy vs. acyclovir or a placebo. At a dosage of 10 mg/kg of body weight twice a day, the test compound significantly inhibited viral replication in vivo, as indicated by a 95% reduction in serum woodchuck hepatitis virus DNA levels and by a 54% reduction in levels of woodchuck hepatitis virus replicative intermediates in the liver. Higher doses were somewhat less effective. In contrast, 20 mg of acyclovir/kg twice daily, a 5.3-fold-higher molar dosage, had no demonstrable activity against woodchuck hepatitis virus. Oral 1-O-hexadecylpropanediol-3-P-acyclovir appeared to be safe and effective in chronic woodchuck hepatitis virus infection.

IT 59277-89-3, Acyclovir
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiviral activities of oral 1-O-hexadecylpropanediol-3-phosphoacyclovir and acyclovir in woodchucks with chronic woodchuck hepatitis virus infection)

RN 59277-89-3 HCAPLUS

CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]- (CA INDEX NAME)



REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 4 OF 38 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2000:182395 HCAPLUS <<LOGINID::20070502>>

DOCUMENT NUMBER: 132:342844

TITLE: Efficacy of topical acyclovir monophosphate, acyclovir, or penciclovir in orofacial HSV-1 infections of mice and genital HSV-2 infections of guinea pigs

AUTHOR(S): Kern, Earl R.; Palmer, Joyce; Szczech, George; Painter, George; Hostetler, Karl Y.

CORPORATE SOURCE: University of Alabama School of Medicine, Birmingham, AL, 35294-2170, USA

SOURCE: Nucleosides, Nucleotides & Nucleic Acids (2000), 19(1 & 2), 501-513
CODEN: NNNAFY; ISSN: 1525-7770

PUBLISHER: Marcel Dekker, Inc.

DOCUMENT TYPE: Journal

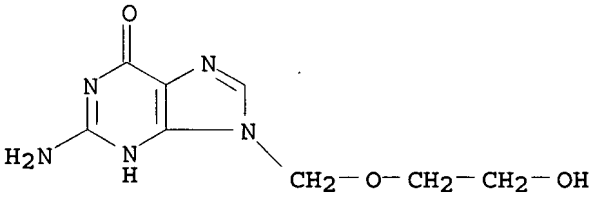
LANGUAGE: English

AB The purpose of these studies was to compare the efficacy of acyclovir monophosphate (ACVMP), acyclovir (ACV), or penciclovir (PCV) against HSV-1 in an orofacial infection of mice and against ACV sensitive and resistant genital HSV-2 infections of guinea pigs. Treatment was initiated 24, 48, or 72 h post inoculation with 5% ACVMP, 5% ACV (Zovirax) or 1% PCV (Denavir). In all expts., similar efficacy was obtained for ACVMP and ACV, whereas PCV was considerably less effective.

IT 59277-89-3, Zovirax 66341-16-0, Acyclovir monophosphate
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(efficacy of topical acyclovir monophosphate, acyclovir, or penciclovir in orofacial HSV-1 infections of mice and genital HSV-2 infections of guinea pigs)

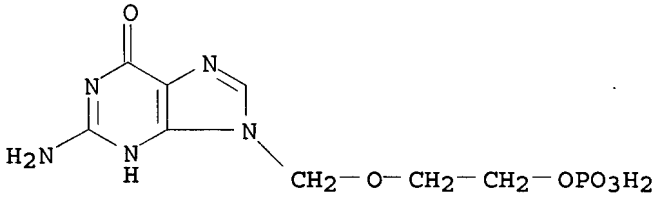
RN 59277-89-3 HCAPLUS

CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]- (CA INDEX NAME)



RN 66341-16-0 HCAPLUS

CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[[2-(phosphonooxy)ethoxy]methyl]- (CA INDEX NAME)



REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 5 OF 38 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1999:310240 HCAPLUS <<LOGINID::20070502>>

DOCUMENT NUMBER: 131:110946

TITLE: Interaction of the recombinant Herpes Simplex Virus type 1 thymidine kinase with thymidine and aciclovir: a kinetic study

AUTHOR(S): Kussmann-Gerber, Susanna; Wurth, Christine; Scapozza, Leonardo; Pilger, Beatrice D.; Pliska, Vladimir; Folkers, Gerd

CORPORATE SOURCE: Department of Pharmacy, Swiss Federal Institute of Technology (ETH), Zurich, CH-8057, Switz.

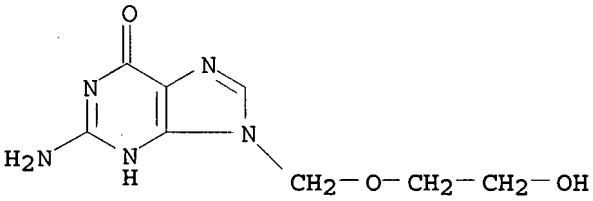
SOURCE: Nucleosides & Nucleotides (1999), 18(3), 311-330

CODEN: NUNUD5; ISSN: 0732-8311
PUBLISHER: Marcel Dekker, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Herpes Simplex Virus type 1 thymidine kinase (HSV 1·TK) is a key target for antiviral therapy and it phosphorylates a broad spectrum of nucleosides and nucleotides. The authors report the results from kinetic and inhibition expts. with HSV 1 TK, and show that there is a preferred, but not exclusive, binding order of substrates, i.e. dT binds prior to ATP. Furthermore, the results provide new informations on the mechanism of binding suggesting that HSV1 TK undergoes conformational changes during the catalytic cycle.

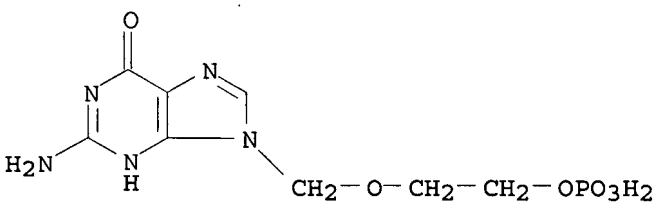
IT 59277-89-3, Aciclovir
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(interaction of recombinant Herpes Simplex Virus type 1 thymidine kinase with thymidine and aciclovir in kinetic study in relation to ATP binding and structure)

RN 59277-89-3 HCAPLUS
CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]- (CA INDEX NAME)



IT 66341-16-0, Acyclovir monophosphate
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(interaction of recombinant Herpes Simplex Virus type 1 thymidine kinase with thymidine and aciclovir in kinetic study in relation to ATP binding and structure)

RN 66341-16-0 HCAPLUS
CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[[2-(phosphonooxy)ethoxy]methyl]- (CA INDEX NAME)



REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 6 OF 38 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:175589 HCAPLUS <<LOGINID::20070502>>
DOCUMENT NUMBER: 130:218263
TITLE: Nucleoside analog phosphates for topical use in the treatment of herpes virus infections

INVENTOR(S): Hostetler, Karl Y.
PATENT ASSIGNEE(S): USA
SOURCE: U.S., 19 pp., Cont.-in-part of U.S. 5,580,571.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

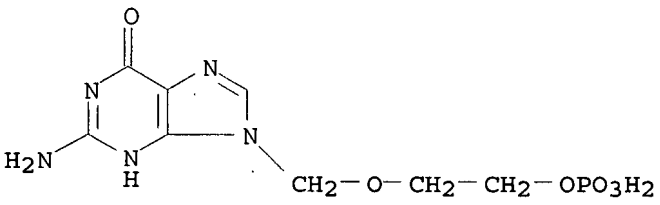
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5879700	A	19990309	US 1995-480456	19950607 <--
US 5580571	A	19961203	US 1993-60258	19930512 <--
CA 2222154	A1	19961219	CA 1996-2222154	19960606 <--
WO 9640088	A1	19961219	WO 1996-US10085	19960606 <--
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
AU 9663842	A	19961230	AU 1996-63842	19960606 <--
EP 831794	A1	19980401	EP 1996-923289	19960606 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
CN 1192138	A	19980902	CN 1996-195922	19960606 <--
JP 11507642	T	19990706	JP 1997-502194	19960606 <--
CN 1221609	A	19990707	CN 1998-123863	19981030 <--

PRIORITY APPLN. INFO.:		
US 1991-777683	B2	19911015
US 1993-60258	A2	19930512
US 1995-480456	A	19950607
WO 1996-US10085	W	19960606

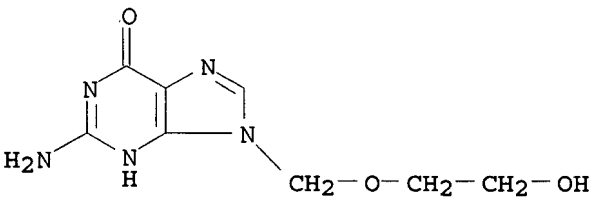
AB Compns. for topical use in herpes virus infections comprise anti-herpes nucleoside analog phosphate esters, e.g. acyclovir monophosphate, acyclovir diphosphate, and acyclovir triphosphate which show increased activity against native strains of herpes virus as well as against resistant strains, particularly thymidine kinase neg. strains of virus. Also disclosed are methods for treatment of herpes infections with nucleoside phosphates. Anti-herpes nucleoside analogs phosphate esters include the phosphoramidates and phosphothiorates, as well as polyphosphates comprising C and S bridging atoms.

IT 66341-16-0P, Acyclovir monophosphate
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(nucleoside analog phosphates for topical use in treatment of herpes virus infections)

RN 66341-16-0 HCAPLUS
CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[[2-(phosphonooxy)ethoxy]methyl]- (CA INDEX NAME)



IT 59277-89-3, Acyclovir
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction; nucleoside analog phosphates for topical use in treatment of herpes virus infections)
RN 59277-89-3 HCAPLUS
CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]- (CA INDEX NAME)



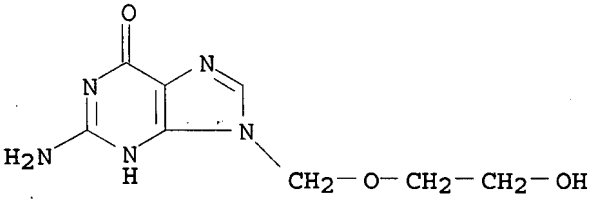
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 7 OF 38 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:588895 HCAPLUS <<LOGINID::20070502>>
DOCUMENT NUMBER: 129:298069
TITLE: Superior cytotoxicity with ganciclovir compared with acyclovir and 1-β-D-arabinofuranosylthymine in herpes simplex virus-thymidine kinase-expressing cells: a novel paradigm for cell killing
AUTHOR(S): Rubsam, Laura Z.; Davidson, Beverly L.; Shewach, Donna S.
CORPORATE SOURCE: Department of Pharmacology, University of Michigan Medical Center, Ann Arbor, MI, 48109-0504, USA
SOURCE: Cancer Research (1998), 58(17), 3873-3882
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Enzyme-prodrug therapy using ganciclovir and herpes simplex virus-thymidine kinase (HSV-TK) has demonstrated excellent antitumor activity in many different types of malignant cells. Previously, the authors noted that ganciclovir was substantially more cytotoxic than other HSV-TK substrates. Therefore, the authors embarked on a study to determine the basis for the superior cytotoxicity of ganciclovir. In U251tk human glioblastoma cells that stably express HSV-TK, ganciclovir elicited a >4 log cell kill instead of the ≤1.5 log cell kill mediated by two other HSV-TK substrates, 1-β-D-arabinofuranosylthymine (araT) and acyclovir. Study of the metabolism of these drugs demonstrated that acyclovir was poorly phosphorylated to its active triphosphate with DNA incorporation below the limit of detection, which may explain the <1 log cell kill in these cells. Lower levels of ganciclovir triphosphate accumulated compared with araT triphosphate (araTTP) under conditions that induced ≥1 log cell kill (67 vs. 1235 pmol/107 cells, resp.), and the half-life for the triphosphate of ganciclovir was shorter than that of araT (terminal half-lives of 15 and 41 h, resp.). Incorporation of ganciclovir monophosphate into DNA was less than that of araT monophosphate, and both analogs were retained in DNA for ≥48 h. Thus, the superior cytotoxicity of ganciclovir was not due to enhanced metabolism to active forms. Highly cytotoxic concns. of ganciclovir produced only weak inhibition of DNA synthesis. This allowed cells to proceed through S and G2-M phases during and after drug exposure, resulting in a

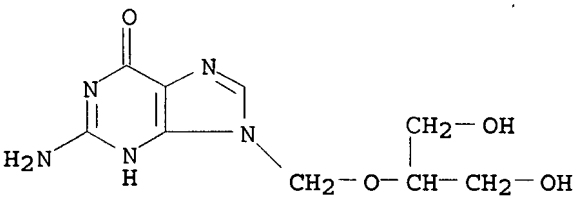
doubling of cell number by 48 h after drug washout. As they attempted to progress through the cell cycle a second time, ganciclovir-treated cells accumulated in early S-phase and remained there until cell death, suggesting that ganciclovir incorporation in the DNA template was important for cytotoxicity. In contrast, strong inhibition of DNA synthesis by araTTP prevented cells from traversing the cell cycle for at least 12 h after drug washout, when the active metabolite was largely degraded. AraT-treated cells were unable to divide for at least 72 h after drug exposure, at which point the surviving cells displayed a normal cell cycle distribution pattern. Based on the results presented here, the authors propose a novel paradigm in which the ability of ganciclovir to incorporate into DNA without inhibiting progression through S-phase, combined with high cytotoxicity for incorporated ganciclovir monophosphate, produces multilog cytotoxicity.

IT 59277-89-3, Acyclovir 82410-32-0, Ganciclovir
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(superior cytotoxicity with ganciclovir compared with acyclovir and D-arabinofuranosylthymine in herpes simplex virus-thymidine kinase-expressing cells in relation to metabolism and incorporation into DNA and apoptosis)

RN 59277-89-3 HCAPLUS
CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]- (CA INDEX NAME)



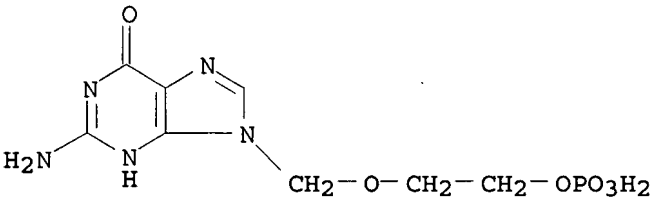
RN 82410-32-0 HCAPLUS
CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]- (CA INDEX NAME)



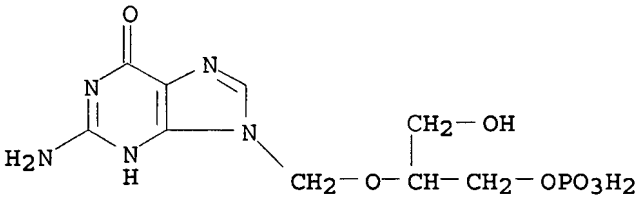
IT 66341-16-0, Acyclovir monophosphate
86761-39-9
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(superior cytotoxicity with ganciclovir compared with acyclovir and D-arabinofuranosylthymine in herpes simplex virus-thymidine kinase-expressing cells in relation to metabolism and incorporation into DNA and apoptosis)

RN 66341-16-0 HCAPLUS
CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[[2-(phosphonooxy)ethoxy]methyl]-

(CA INDEX NAME)



RN 86761-39-9 HCAPLUS
CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[[1-(hydroxymethyl)-2-(phosphonooxy)ethoxy]methyl]- (CA INDEX NAME)



REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 8 OF 38 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:516837 HCAPLUS <<LOGINID::20070502>>
DOCUMENT NUMBER: 129:239501
TITLE: Mode of action of (1'S,2'R)-9-{[1',2'-bis(hydroxymethyl)cycloprop-1'-yl]methyl}guanine (A-5021) against herpes simplex virus Type 1 and Type 2 and varicella-zoster virus
AUTHOR(S): Ono, Nobukazu; Iwayama, Satoshi; Suzuki, Katsuya; Sekiyama, Takaaki; Nakazawa, Harumi; Tsuji, Takashi; Okunishi, Masahiko; Daikoku, Tohru; Nishiyama, Yukihiro
CORPORATE SOURCE: Life Science Laboratories, Ajinomoto Co., Inc., Yokohama, 244, Japan
SOURCE: Antimicrobial Agents and Chemotherapy (1998), 42(8), 2095-2102
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

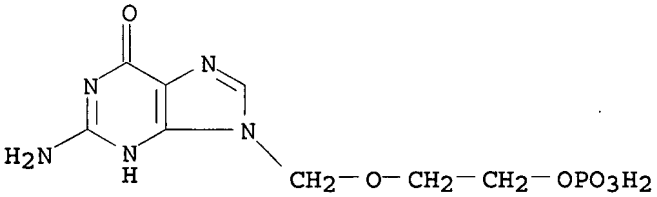
AB The mode of action of (1'S,2'R)-9-{[1',2'-bis(hydroxymethyl)cycloprop-1'-yl]methyl}guanine (A-5021) against herpes simplex virus type 1 (HSV-1), HSV-2, and varicella-zoster virus (VZV) was studied. A-5021 was monophosphorylated at the 2' site by viral thymidine kinases (TKs). The 50% inhibitory values for thymidine phosphorylation of A-5021 by HSV-1 TK and HSV-2 TK were comparable to those for penciclovir (PCV) and lower than those for acyclovir (ACV). Of these three agents, A-5021 inhibited VZV TK most efficiently. A-5021 was phosphorylated to a mono-, di-, and triphosphate in MRC-5 cells infected with HSV-1, HSV-2, and VZV. A-5021 triphosphte accumulated more than ACV triphosphate but less than PCV triphosphate in MRC-5 cells infected with HSV-1 or VZV, whereas HSV-2-infected MRC-5 cells had comparable levels of A-5021 and ACV triphosphates. The intracellular half-life of A-5021 triphosphate was

considerably longer than that of ACV triphosphate and shorter than that of PCV triphosphate. A-5021 triphosphate competitively inhibited HSV DNA polymerases with respect to dGTP. Inhibition was strongest with ACV triphosphate, followed by A-5021 triphosphate and then (R,S)-PCV triphosphate. A DNA chain elongation experiment revealed that A-5021 triphosphate was incorporated into DNA instead of dGTP and terminated elongation, although limited chain extension was observed Thus, the strong antiviral activity of A-5021 appears to depend on a more rapid and stable accumulation of its triphosphate in infected cells than that of ACV and on stronger inhibition of viral DNA polymerase by its triphosphate than that of PCV.

IT 66341-16-0P, Acyclovir monophosphate
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
((1'S,2'R)-9-{[1',2'-bis(hydroxymethyl)cycloprop-1'-yl]methyl}guanine (A-5021) action against herpes simplex virus Type 1 and Type 2 and varicella-zoster virus)

RN 66341-16-0 HCAPLUS

CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[[2-(phosphonooxy)ethoxy]methyl]- (CA INDEX NAME)



REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 9 OF 38 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1997:804941 HCAPLUS <<LOGINID::20070502>>

DOCUMENT NUMBER: 128:123480

TITLE: Synthesis, biological activity and decomposition studies of amino acid phosphomonoester amidates of acyclovir

AUTHOR(S): Abraham, Timothy W.; Mcintee, Edward J.; Iyer, Vidhya V.; Schinazi, Raymond F.; Wagner, Carston R.

CORPORATE SOURCE: Department of Medicinal Chemistry, College of Pharmacy, University of Minnesota, Minneapolis, MN, 55455, USA

SOURCE: Nucleosides & Nucleotides (1997), 16(10 & 11), 2079-2092
CODEN: NUNUD5; ISSN: 0732-8311

PUBLISHER: Marcel Dekker, Inc.

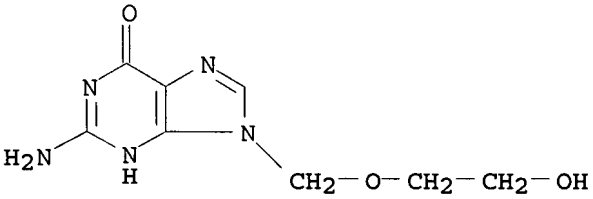
DOCUMENT TYPE: Journal

LANGUAGE: English

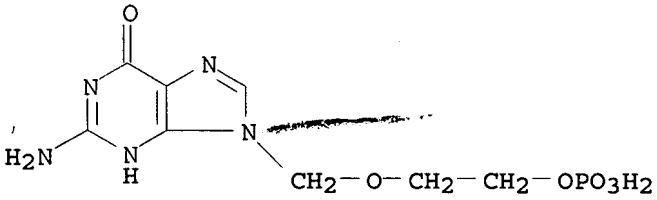
AB Highly stable and water soluble amino acid phosphomonoester amidates of acyclovir (ACV) were synthesized and shown to function predominantly as prodrugs of ACV and not acyclovir monophosphate (ACV-MP) with activities within two fold of the amino acid prodrug of ACV, valaciclovir (VACV). Metabolism studies revealed that incubation of cell-free exts. of Vero cells with the L-leucine phosphomonoester amidate of ACV (3c), resulted in a burst of ACV-MP production followed by the rapid generation of ACV.

IT 59277-89-3, Acyclovir
RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation and anti-HSV activity of amino acid phosphomonoester amidates of acyclovir)
RN 59277-89-3 HCAPLUS
CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]- (CA INDEX NAME)



IT 66341-16-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and anti-HSV activity of amino acid phosphomonoester amidates of acyclovir)
RN 66341-16-0 HCAPLUS
CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[[2-(phosphonooxy)ethoxy]methyl]- (CA INDEX NAME)



REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 10 OF 38 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:121416 HCAPLUS <<LOGINID::20070502>>
DOCUMENT NUMBER: 126:135594
TITLE: Acyclovir derivatives for topical use
INVENTOR(S): Hostetler, Karl Y.
PATENT ASSIGNEE(S): Hostetler, Karl Y., USA
SOURCE: PCT Int. Appl., 34 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9640088	A1	19961219	WO 1996-US10085	19960606 <--
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
US 5879700	A	19990309	US 1995-480456	19950607 <--

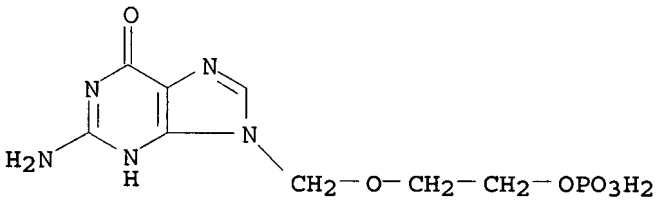
AU 9663842	A	19961230	AU 1996-63842		19960606 <--
EP 831794	A1	19980401	EP 1996-923289		19960606 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI					
JP 11507642	T	19990706	JP 1997-502194		19960606 <--
PRIORITY APPLN. INFO.:			US 1995-480456	A	19950607
			US 1991-777683	B2	19911015
			US 1993-60258	A2	19930512
			WO 1996-US10085	W	19960606

AB The invention involves compns. for topical use in herpes virus infections comprising anti-herpes nucleoside analog phosphate esters, such as acyclovir monophosphate, acyclovir diphosphate, and acyclovir triphosphate, which show increased activity against native strains of herpes virus as well as against resistant strains, particularly thymidine kinase neg. strains of virus. Anti-herpes nucleoside analogs phosphate esters include the phosphoramidates and phosphothiorates, as well as polyphosphates comprising C and S bridging atoms.

IT 66341-16-0, Acyclovir monophosphate
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); PROC (Process); RACT (Reactant or reagent); USES (Uses)
(acyclovir derivs. for topical use against herpes virus infections)

RN 66341-16-0 HCAPLUS

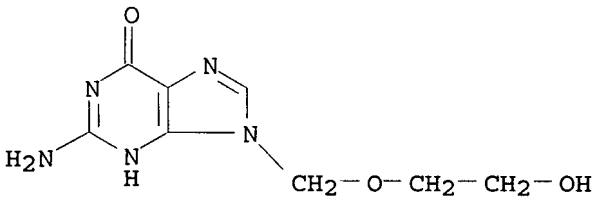
CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[[2-(phosphonooxy)ethoxy]methyl]- (CA INDEX NAME)



IT 59277-89-3, Acyclovir
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(acyclovir derivs. for topical use against herpes virus infections)

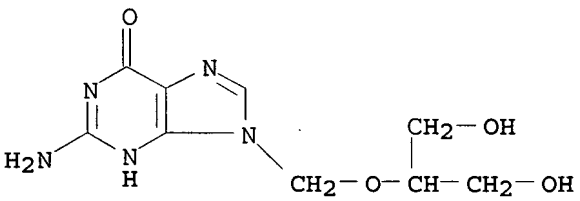
RN 59277-89-3 HCAPLUS

CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]- (CA INDEX NAME)



IT 82410-32-0

RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(acyclovir derivs. for topical use against herpes virus infections)
RN 82410-32-0 HCAPLUS
CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]- (CA INDEX NAME)



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        298557 KINASE
                 (KINASE OR KINASES)
L11       9845 THYMIDINE KINASE
                 (THYMIDINE(W)KINASE)

=> d his

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L1              1 S E3

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     FILE 'HCAPLUS' ENTERED AT 16:02:09 ON 02 MAY 2007
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L4         276194 S L2 OR L3
L5              1 S L4 AND L1

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     FILE 'HCAPLUS' ENTERED AT 16:07:58 ON 02 MAY 2007
L6          6746 S  (59277-89-3 OR 66341-16-0 OR 82410-32-0 OR 86761-39-9 OR 104
                E HERPES+ALL/CT
L7          2471 S L6 AND (HERPES OR "HERPES" OR "INFECTION" (L) "HERPES" OR "SK
L8           113 S ACYCLOVIR ?PHOSPHATE?
L9            40 S L8 AND L7
L10           38 S L9 AND 1800<=PY<=2003
L11         9845 S THYMIDINE KINASE

=> s l11 and l10
L12           24 L11 AND L10
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                 (KINASE OR KINASES)
        538149 INHIBITOR
        542706 INHIBITORS
        846539 INHIBITOR
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=> s l13 and l12
L14          0 L13 AND L12

=> d l12 ti 1-24

L12  ANSWER 1 OF 24  HCAPLUS  COPYRIGHT 2007 ACS on STN
TI   Antiviral activity of cyclosaligenyl prodrugs of acyclovir, carbovir, and
     abacavir

L12  ANSWER 2 OF 24  HCAPLUS  COPYRIGHT 2007 ACS on STN
TI   Antiviral activities of oral 1-O-hexadecylpropanediol-3-phosphoacyclovir
     and acyclovir in woodchucks with chronic woodchuck hepatitis virus
     infection

L12  ANSWER 3 OF 24  HCAPLUS  COPYRIGHT 2007 ACS on STN
TI   Interaction of the recombinant Herpes Simplex Virus type 1
     thymidine kinase with thymidine and aciclovir: a kinetic
     study

L12  ANSWER 4 OF 24  HCAPLUS  COPYRIGHT 2007 ACS on STN
TI   Nucleoside analog phosphates for topical use in the treatment of
     herpes virus infections

L12  ANSWER 5 OF 24  HCAPLUS  COPYRIGHT 2007 ACS on STN
TI   Superior cytotoxicity with ganciclovir compared with acyclovir and
     1-β-D-arabinofuranosylthymine in  herpes simplex virus-
     thymidine kinase-expressing cells: a novel paradigm for
     cell killing

L12  ANSWER 6 OF 24  HCAPLUS  COPYRIGHT 2007 ACS on STN
TI   Mode of action of (1'S,2'R)-9-{[1',2'-bis(hydroxymethyl)cycloprop-1'-
     yl]methyl}guanine (A-5021) against herpes simplex virus Type 1
     and Type 2 and varicella-zoster virus

L12  ANSWER 7 OF 24  HCAPLUS  COPYRIGHT 2007 ACS on STN
TI   Acyclovir derivatives for topical use

L12  ANSWER 8 OF 24  HCAPLUS  COPYRIGHT 2007 ACS on STN
TI   Historical aspects of anti-herpesvirus research leading to the discovery
     of acyclovir

L12  ANSWER 9 OF 24  HCAPLUS  COPYRIGHT 2007 ACS on STN
TI   Nucleoside analogs for topical use in herpesvirus infections

L12  ANSWER 10 OF 24  HCAPLUS  COPYRIGHT 2007 ACS on STN
TI   Herpes simplex virus resistance to acyclovir: Clinical relevance
```

L12 ANSWER 11 OF 24 HCAPLUS COPYRIGHT 2007 ACS on STN
TI A comparative study of the in vitro and in vivo antiviral activities of acyclovir and penciclovir

L12 ANSWER 12 OF 24 HCAPLUS COPYRIGHT 2007 ACS on STN
TI Acyclovir derivatives and other nucleoside analogs for topical treatment of herpes infection

L12 ANSWER 13 OF 24 HCAPLUS COPYRIGHT 2007 ACS on STN
TI Acyclovir diphosphate dimyristoylglycerol: a phospholipid prodrug with activity against acyclovir-resistant herpes simplex virus

L12 ANSWER 14 OF 24 HCAPLUS COPYRIGHT 2007 ACS on STN
TI Inhibition of herpes simplex virus type 1 DNA polymerase by [1R(1α,2β,3α)]-9-[2,3-bis(hydroxymethyl)cyclobutyl]guanin e

L12 ANSWER 15 OF 24 HCAPLUS COPYRIGHT 2007 ACS on STN
TI Herpes simplex virus type 1 DNA polymerase. Mechanism of inhibition by acyclovir triphosphate

L12 ANSWER 16 OF 24 HCAPLUS COPYRIGHT 2007 ACS on STN
TI Effects of various nucleosides on antiviral activity and metabolism of 1-β-D-arabinofuranosyl-E-5-(2-bromovinyl)uracil against herpes simplex virus types 1 and 2

L12 ANSWER 17 OF 24 HCAPLUS COPYRIGHT 2007 ACS on STN
TI Antiviral activities of guanosine analogs in guinea pig embryonic fibroblasts

L12 ANSWER 18 OF 24 HCAPLUS COPYRIGHT 2007 ACS on STN
TI Solution conformations of some acyclonucleoside and nucleotide analogs of antiviral acyclonucleosides, and their substrate/inhibitor properties in several enzyme systems

L12 ANSWER 19 OF 24 HCAPLUS COPYRIGHT 2007 ACS on STN
TI Cooperative effects between two acyclovir resistance loci in herpes simplex virus

L12 ANSWER 20 OF 24 HCAPLUS COPYRIGHT 2007 ACS on STN
TI Selectivity of antiviral effectiveness derived from differences of herpes simplex virus-coded thymidine kinases

L12 ANSWER 21 OF 24 HCAPLUS COPYRIGHT 2007 ACS on STN
TI A perspective on resistance to acyclovir in herpes simplex virus

L12 ANSWER 22 OF 24 HCAPLUS COPYRIGHT 2007 ACS on STN
TI Acyclovir-resistant mutants of herpes simplex virus type 1 express altered DNA polymerase or reduced acyclovir phosphorylating activities

L12 ANSWER 23 OF 24 HCAPLUS COPYRIGHT 2007 ACS on STN
TI Laboratory studies on acyclovir

L12 ANSWER 24 OF 24 HCAPLUS COPYRIGHT 2007 ACS on STN
TI The chemotherapeutic exploitation of virus-specified enzymes

=> s cidofovir
L15 684 CIDOFOVIR

=> s l15 and l7

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L16         89 L15 AND L7

=> s l16 and l10
L17          0 L16 AND L10

=> s ganciclovir monophosphate
             5 GANCILOVIR
         31705 MONOPHOSPHATE
          4114 MONOPHOSPHATES
         34622 MONOPHOSPHATE
                 (MONOPHOSPHATE OR MONOPHOSPHATES)
L18          0 GANCILOVIR MONOPHOSPHATE
                 (GANCILOVIR(W)MONOPHOSPHATE)

=> s ganciclovir
L19       3504 GANCICLOVIR

=> s ganciclovir monophosphate
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         31705 MONOPHOSPHATE
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         34622 MONOPHOSPHATE
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L20         11 GANCICLOVIR MONOPHOSPHATE
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=> s l20 and l7
L21          2 L20 AND L7

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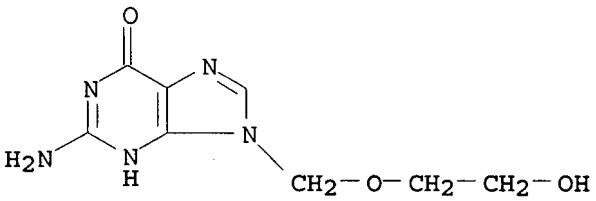
L21  ANSWER 1 OF 2  HCAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:        1998:588895  HCAPLUS <<LOGINID::20070502>>
DOCUMENT NUMBER:         129:298069
TITLE:                   Superior cytotoxicity with ganciclovir compared with
                         acyclovir and 1-β-D-arabinofuranosylthymine in
                         herpes simplex virus-thymidine
                         kinase-expressing cells: a novel paradigm for cell
                         killing
AUTHOR(S):               Rubsam, Laura Z.; Davidson, Beverly L.; Shewach, Donna
                         S.
CORPORATE SOURCE:        Department of Pharmacology, University of Michigan
                         Medical Center, Ann Arbor, MI, 48109-0504, USA
SOURCE:                  Cancer Research (1998), 58(17), 3873-3882
                         CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER:               American Association for Cancer Research
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   Enzyme-prodrug therapy using ganciclovir and herpes simplex
     virus-thymidine kinase (HSV-TK) has demonstrated excellent antitumor
     activity in many different types of malignant cells.  Previously, the
     authors noted that ganciclovir was substantially more cytotoxic than other
     HSV-TK substrates.  Therefore, the authors embarked on a study to determine the
     basis for the superior cytotoxicity of ganciclovir.  In U251tk human
     glioblastoma cells that stably express HSV-TK, ganciclovir elicited a >4
     log cell kill instead of the ≤1.5 log cell kill mediated by two
     other HSV-TK substrates, 1-β-D-arabinofuranosylthymine (araT) and
     acyclovir.  Study of the metabolism of these drugs demonstrated that acyclovir
     was poorly phosphorylated to its active triphosphate with DNA
     incorporation below the limit of detection, which may explain the <1 log
     cell kill in these cells.  Lower levels of ganciclovir triphosphate
     accumulated compared with araT triphosphate (araTTP) under conditions that
     induced ≥1 log cell kill (67 vs. 1235 pmol/107 cells, resp.), and
```

the half-life for the triphosphate of ganciclovir was shorter than that of araT (terminal half-lives of 15 and 41 h, resp.). Incorporation of ganciclovir monophosphate into DNA was less than that of araT monophosphate, and both analogs were retained in DNA for ≥48 h. Thus, the superior cytotoxicity of ganciclovir was not due to enhanced metabolism to active forms. Highly cytotoxic concns. of ganciclovir produced only weak inhibition of DNA synthesis. This allowed cells to proceed through S and G2-M phases during and after drug exposure, resulting in a doubling of cell number by 48 h after drug washout. As they attempted to progress through the cell cycle a second time, ganciclovir-treated cells accumulated in early S-phase and remained there until cell death, suggesting that ganciclovir incorporation in the DNA template was important for cytotoxicity. In contrast, strong inhibition of DNA synthesis by araTTP prevented cells from traversing the cell cycle for at least 12 h after drug washout, when the active metabolite was largely degraded. AraT-treated cells were unable to divide for at least 72 h after drug exposure, at which point the surviving cells displayed a normal cell cycle distribution pattern. Based on the results presented here, the authors propose a novel paradigm in which the ability of ganciclovir to incorporate into DNA without inhibiting progression through S-phase, combined with high cytotoxicity for incorporated ganciclovir monophosphate, produces multilog cytotoxicity.

IT 59277-89-3, Acyclovir 82410-32-0, Ganciclovir
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(superior cytotoxicity with ganciclovir compared with acyclovir and D-arabinofuranosylthymine in herpes simplex virus-thymidine kinase-expressing cells in relation to metabolism and incorporation into DNA and apoptosis)

RN 59277-89-3 HCAPLUS
CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]- (CA INDEX NAME)



RN 82410-32-0 HCAPLUS
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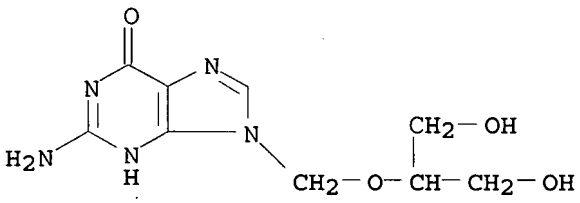

IT 66341-16-0, Acyclovir monophosphate 86761-39-9
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation,

substance identification.

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=> s foscarnet
L23         857 FOSCARNET

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L24         121 L23 AND L7

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L25          93 L24 AND 1800<=PY<=2003

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MISSING OPERATOR L25 IBIB
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nested terms that are not separated by a logical operator.

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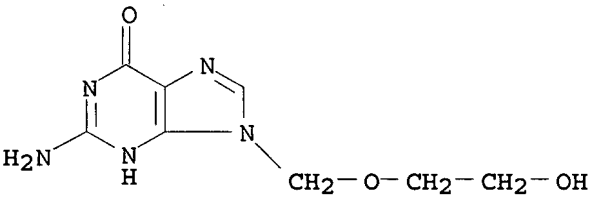
L25  ANSWER 1 OF 93  HCAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:         2003:741595  HCAPLUS <<LOGINID::20070502>>
DOCUMENT NUMBER:          140:104511
TITLE:                    Comparison of HSV-1 thymidine kinase-dependent and
                          -independent inhibition of replication-competent
                          adenoviral vectors by a panel of drugs
AUTHOR(S):                Wildner, Oliver; Hoffmann, Dennis; Jogler, Christian;
                          Ueberla, Klaus
CORPORATE SOURCE:         Bldg. MA, Abteilung fuer Molekulare und Medizinische
                          Virologie, Ruhr-Universitaet Bochum, Bochum, D-44801,
                          Germany
SOURCE:                   Cancer Gene Therapy (2003), 10(10), 791-802
                          CODEN: CGTHEG; ISSN: 0929-1903
PUBLISHER:                Nature Publishing Group
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB   Replication-competent adenoviral vectors hold the promise to be more
     efficient gene delivery vehicles than their replication-deficient
     counterparts, but they are also associated with a higher risk for adverse
     effects, especially in light of the fact that there is no established effective
     therapy for serious, disseminated adenovirus infection.  To
     assess whether the therapeutic options to inhibit adenoviral replication
     can be enhanced by expressing a suicide gene, we examined the antiadenoviral
     effects of 15 drugs against wild-type adenovirus type 5 (Ad5) and an
     Ad5-based replication-competent vector expressing herpes simplex
     virus-1 thymidine kinase (HSV-tk) (Ad.OW34) using a real-time polymerase
     chain reaction -based assay and flow cytometry.  Ad5 and Ad.OW34 were
     highly susceptible to the fluorinated pyrimidine analogs
     5-fluoro-2'-deoxyuridine (FUdR), 5-fluorouridine (FUR), and
     trifluorothymidine (TFT), with a mean 50% inhibitory concentration (IC50) ranging
     from 0.12 to 0.32 μM. The mean IC50 of ribavirin and cidofovir (CDV)
     for Ad5, the most frequently used drugs to treat adenovirus disease, was
     6.87 and 3.19 μM, resp.  In contrast to Ad5, the Ad.OW34 vector was
     susceptible to (E)-5-(2-bromovinyl)-2'-deoxyuridine (BVdU, IC50 0.09
     μM), ganciclovir (GCV, IC50 0.19 μM), and acyclovir (ACV, IC50 32.04
     μM).  Addnl., we demonstrated in an animal model that Ad.OW34 vector
     replication can be inhibited significantly by GCV, CDV, and TFT by 35.2,
     7.7, and 3.7-fold, resp., compared to untreated animals.  The observed
     antiadenoviral effects were primarily not through cell killing, since the
     in vitro 50% cytotoxic concns. (CC50) were more than 1000 times higher
     than the antiadenoviral IC50 of the drugs examined, even in cells stably
```

expressing HSV-tk. Since for HSV-tk-dependent inhibition of adenoviral vectors, stability of HSV-tk expression is crucial, we examined Ad.OW34 vector stability, by passaging the vector 10 times serially in the presence of 10 μM GCV. The HSV-tk/GCV system neither changed the susceptibility of Ad.OW34 to GCV significantly nor detectable vector rearrangements occurred, suggesting that the system might be suitable as a fail-safe mechanism to stop adenoviral vector replication.

IT 59277-89-3, Acyclovir 82410-32-0, Ganciclovir
113852-37-2, Cidofovir
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of replication competent adenoviral vectors by a panel of drugs)

RN 59277-89-3 HCAPLUS
CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]- (CA INDEX NAME)



RN 82410-32-0 HCAPLUS
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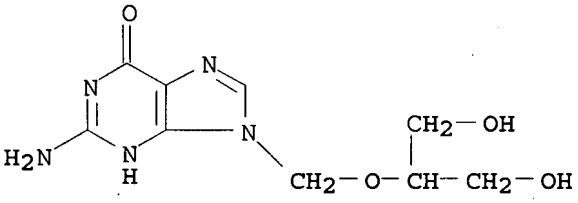
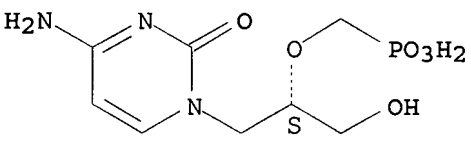


RN 113852-37-2 HCAPLUS
CN Phosphonic acid, P-[[(1S)-2-(4-amino-2-oxo-1(2H)-pyrimidinyl)-1-(hydroxymethyl)ethoxy]methyl]- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 101 THERE ARE 101 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

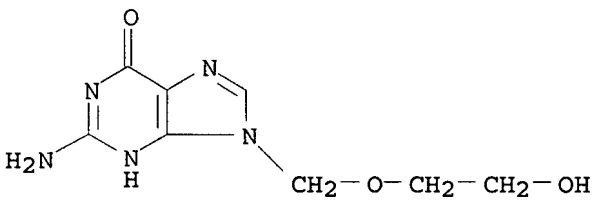
L25 ANSWER 2 OF 93 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:543502 HCAPLUS <<LOGINID::20070502>>

DOCUMENT NUMBER: 139:357783
TITLE: Current and potential therapies for the treatment of herpesvirus infections
AUTHOR(S): Villarreal, Elcira C.
CORPORATE SOURCE: Lilly Centre for Women's Health, Eli Lilly and Company, Indianapolis, IN, 46285, USA
SOURCE: Progress in Drug Research (2003), 60, 263-307
CODEN: FAZMAE; ISSN: 0071-786X
PUBLISHER: Birkhaeuser Verlag
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Human herpesviruses are found worldwide and are among the most frequent causes of viral infections in immunocompetent as well as in immunocompromised patients. During the past decade and a half a better understanding of the replication and disease-causing state of herpes simplex virus types 1 and 2 (HSV-1 and HSV-2), varicella zoster virus (VZV), and human cytomegalovirus (HCMV) has been achieved due in part to the development of potent antiviral compds. that target these viruses. While some of these antiviral therapies are considered safe and efficacious (acyclovir, penciclovir), some have toxicities associated with them (ganciclovir and foscarnet). In addition, the increased and prolonged use of these compds. in the clin. setting, especially for the treatment of immunocompromised patients, has led to the emergence of viral resistance against most of these drugs. While resistance is not a serious issue for immunocompetent individuals, it is a real concern for immunocompromised patients, especially those with AIDS and the ones that have undergone organ transplantation. All the currently approved treatments target the viral DNA polymerase. It is clear that new drugs that are more efficacious than the present ones, are not toxic, and target a different viral function would be of great use especially for immunocompromised patients. Here, an overview is provided of the diseases caused by the herpesviruses as well as the replication strategy of the better studied members of this family for which treatments are available. We also discuss the various drugs that have been approved for the treatment of some herpesviruses in terms of structure, mechanism of action, and development of resistance. Finally, we present a discussion of viral targets other than the DNA polymerase, for which new antiviral compds. are being considered.

IT 59277-89-3, Acyclovir 82410-32-0, Ganciclovir
RL: ADV (Adverse effect, including toxicity); DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(current and potential therapies for treatment of herpesvirus infections)

RN 59277-89-3 HCAPLUS
CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]- (CA INDEX NAME)



RN 82410-32-0 HCAPLUS
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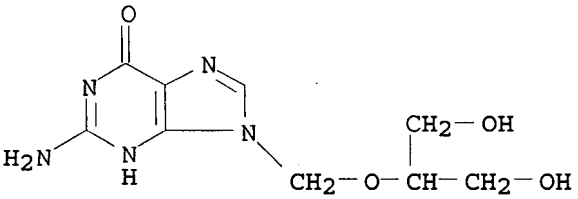

REFERENCE COUNT: 249 THERE ARE 249 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 3 OF 93 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:526763 HCAPLUS <<LOGINID::20070502>>
DOCUMENT NUMBER: 139:175724
TITLE: Drug resistance patterns of recombinant herpes simplex virus DNA polymerase mutants generated with a set of overlapping cosmids and plasmids
AUTHOR(S): Bestman-Smith, Julie; Boivin, Guy
CORPORATE SOURCE: Centre de Recherche en Infectiologie of the Centre Hospitalier Universitaire de Quebec (Pavillon CHUL) and Universite Laval, Quebec, Can.
SOURCE: Journal of Virology (2003), 77(14), 7820-7829
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Herpes simplex virus (HSV) DNA polymerase (Pol) mutations can confer resistance to all currently available antiherpetic drugs. However, discrimination between mutations responsible for drug resistance and those that are part of viral polymorphism can be difficult with current methodologies. A new system is reported for rapid generation of recombinant HSV type 1 (HSV-1) DNA Pol mutants based on transfection of a set of overlapping viral cosmids and plasmids. With this approach, twenty HSV-1 recombinants with single or dual mutations within the DNA pol gene were successfully generated and subsequently evaluated for their susceptibilities to acyclovir (ACV), foscarnet (FOS), cidofovir (CDV), and adefovir (ADV). Mutations within DNA Pol conserved regions II (A719T and S724N), VI (L778M, D780N, and L782I), and I (F891C) were shown to induce cross-resistance to ACV, FOS, and ADV, with two of these mutations (S724N and L778M) also conferring significant reduction in CDV susceptibility. Mutant F891C was associated with the highest levels of resistance towards ACV and FOS and was strongly impaired in its replication capacity. One mutation (D907V) lying outside of the conserved regions was also associated with this ACV-, FOS-, and ADV-resistant phenotype. Some mutations (K522E and Y577H) within the δ-region C were lethal, whereas others (P561S and V573M) induced no resistance to any of the drugs tested. Recombinants harboring mutations within conserved regions V (N961K) and VII (Y941H) were resistant to ACV but susceptible to FOS. Finally, mutations within conserved region III were associated with various susceptibility profiles. This new system allows a rapid and accurate evaluation of the functional role of various DNA Pol mutations, which should translate into improved management of drug-resistant HSV infections.

IT 59277-89-3, Acyclovir 106941-25-7, Adefovir 113852-37-2, Cidofovir
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(drug resistance patterns of recombinant herpes simplex virus

DNA polymerase mutants generated with a set of overlapping cosmids and plasmids)

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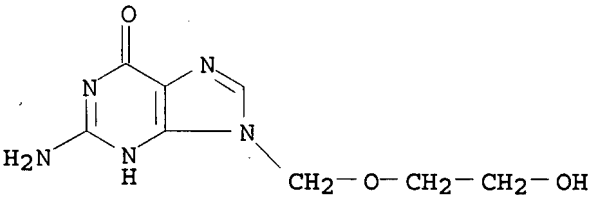

RN 106941-25-7 HCAPLUS
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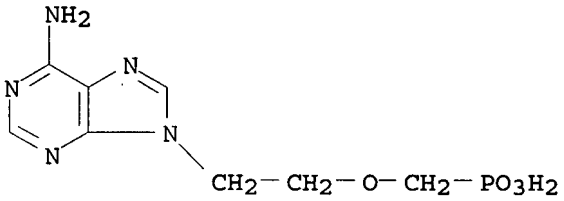

RN 113852-37-2 HCAPLUS
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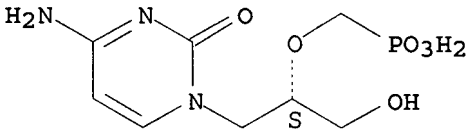
Absolute stereochemistry.



REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 4 OF 93 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:513247 HCAPLUS <<LOGINID::20070502>>
DOCUMENT NUMBER: 139:358071
TITLE: In vitro activities of benzimidazole D- and L-ribonucleosides against herpesviruses
AUTHOR(S): Williams, Stephanie L.; Hartline, Caroll B.; Kushner, Nicole L.; Harden, Emma A.; Bidanset, Deborah J.; Drach, John C.; Townsend, Leroy B.; Underwood, Mark R.; Biron, Karen K.; Kern, Earl R.
CORPORATE SOURCE: University of Alabama School of Medicine, Birmingham, AL, USA
SOURCE: Antimicrobial Agents and Chemotherapy (2003), 47(7), 2186-2192
CODEN: AMACCQ; ISSN: 0066-4804

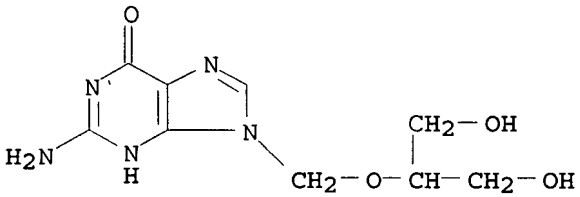
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Herpes simplex virus types 1 and 2 (HSV-1 and HSV-2), varicella-zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), human herpesvirus 6 (HHV-6), and human herpesvirus 8 (HHV-8) are responsible for a number of clin. manifestations in both normal and immunocompromised individuals. The parent benzimidazole ribonucleosides evaluated in this series, 2-bromo-5,6-dichloro-1-(β-D-ribofuranosyl)benzimidazole (BDCRB) and maribavir (1263W94), are potent and selective inhibitors of human CMV replication. These nucleosides act by two different mechanisms. BDCRB blocks the processing and maturation of viral DNA, whereas 1263W94 inhibits the viral enzyme pUL97 and interferes with DNA synthesis. In the present study, we have evaluated the in vitro antiviral activity of BDCRB, an analog, GW275175X (175X), and 1263W94 against the replication of HSV-1, HSV-2, VZV, CMV, EBV, HHV-6, and HHV-8. By using various methodologies, significant activity was observed against human CMV and EBV but not against HSV-1, HSV-2, VZV, HHV-6, or HHV-8. Plaque reduction assays performed on a variety of laboratory and clin. isolates of human CMV indicated that all strains, including those resistant to ganciclovir (GCV) and foscarnet, were sensitive to all three benzimidazole ribonucleosides, with mean 50% effective concentration values of about 1 to 5 μM compared to that of GCV at 6 μM. The toxicity of these compds. in tissue culture cells appeared to be similar to that observed with GCV. These results demonstrate that the benzimidazole ribonucleosides are active against human CMV and EBV and suggest that they may be useful for the treatment of infections caused by these herpesviruses.

IT 82410-32-0, Ganciclovir
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(-resistant strains; in vitro activities of benzimidazole D- and L-ribonucleosides against herpesviruses)

RN 82410-32-0 HCAPLUS

CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]- (CA INDEX NAME)



IT 59277-89-3, Acyclovir 113852-37-2, Cidofovir
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(comparison compound; in vitro activities of benzimidazole D- and L-ribonucleosides against herpesviruses)

RN 59277-89-3 HCAPLUS

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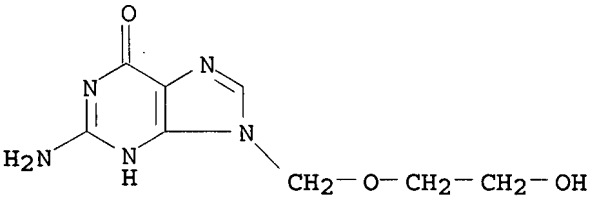
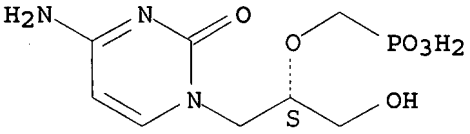


RN 113852-37-2 HCAPLUS
CN Phosphonic acid, P-[[(1S)-2-(4-amino-2-oxo-1(2H)-pyrimidinyl)-1-(hydroxymethyl)ethoxy]methyl]- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 5 OF 93 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:484460 HCAPLUS <<LOGINID::20070502>>
DOCUMENT NUMBER: 139:374303
TITLE: Binding of a N,N'-bisheteryl derivative of dispirotripiperazine to heparan sulfate residues on the cell surface specifically prevents infection of viruses from different families
AUTHOR(S): Schmidtke, M.; Karger, A.; Meerbach, A.; Egerer, R.; Stelzner, A.; Makarov, V.
CORPORATE SOURCE: Institute of Virology and Antiviral Therapy, Friedrich Schiller University of Jena, Jena, D-07745, Germany
SOURCE: Virology (2003), 311(1), 134-143
CODEN: VIRLAX; ISSN: 0042-6822
PUBLISHER: Elsevier Science
DOCUMENT TYPE: Journal
LANGUAGE: English

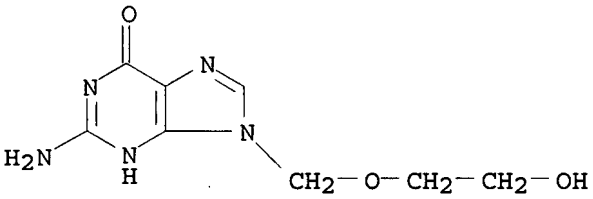
AB N,N'-bisheteryl derivs. of dispirotripiperazine (DSTP) are a novel class of antiviral compds. with some of their representatives very effectively inhibiting the replication of herpes simplex virus type 1 (HSV-1) in cell culture. Using one representative of these compds., the N,N'-bis(1-oxido[1,2,5]oxadiazolo[3,4-d]pyrimidin-7-yl)-3,12-diaza-6,9-diazonia(5,2,5,2)dispirohexadecane dichloride (DSTP 27), we here further tried to elucidate the mol. mechanisms responsible for the antiviral activity. The results from plaque reduction assays under a variety of conditions suggest that inhibition of HSV-1 strain Kupka replication by DSTP 27 occurs at the level of viral attachment by blockade of heparan sulfate (HS) structures on the cell surface that are used as viral receptors. In contrast to heparin and pentosan polysulfate, pretreatment of cells with DSTP 27 resulted in efficient inhibition of viral adsorption and replication persisting several hours after removal of the inhibitor. Specific binding of DSTP 27 to heparin was demonstrated in vitro. Titrns. of gC-pos. and gC-neg. pseudorabies virus (PrV) mutants on HS-pos. and HS-neg. cell lines confirmed that inhibitory action of DSTP 27 is strictly HS dependent. Aside from HSV-1 Kupka and PrV, DSTP 27 efficiently inhibits growth of several HSV-1 and HSV-2 strains, among them aciclovir/foscarnet-resistant strains, human cytomegalovirus, human

respiratory syncytial virus, and human immunodeficiency viruses known to attach to the cell surface via HS.

IT 59277-89-3, Aciclovir
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aciclovir/foscarnet-resistant strains; binding of a N,N'-bisheteryl derivative of dispirotripiperazine to heparan sulfate residues on cell surface specifically prevents infection of viruses from different families)

RN 59277-89-3 HCAPLUS

CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]- (CA INDEX NAME)



REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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FULL ESTIMATED COST	34.15	165.52

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CA SUBSCRIBER PRICE	-3.90	-14.82

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L3 237600 S (9002-89-5 OR 9004-34-6 OR 9005-25-8 OR 9012-36-6 OR 24980-4
L4 276194 S L2 OR L3
L5 1 S L4 AND L1

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                 E HERPES+ALL/CT
L7          2471 S L6 AND (HERPES OR "HERPES" OR "INFECTION" (L) "HERPES" OR "SK
L8           113 S ACYCLOVIR ?PHOSPHATE?
L9            40 S L8 AND L7
L10           38 S L9 AND 1800<=PY<=2003
L11         9845 S THYMIDINE KINASE
L12           24 S L11 AND L10
L13           76 S THYMIDINE KINASE INHIBITOR
L14            0 S L13 AND L12
L15          684 S CIDOFOVIR
L16           89 S L15 AND L7
L17            0 S L16 AND L10
L18            0 S GANCILOVIR MONOPHOSPHATE
L19         3504 S GANCICLOVIR
L20           11 S GANCICLOVIR MONOPHOSPHATE
L21            2 S L20 AND L7

     FILE 'STNGUIDE' ENTERED AT 16:16:23 ON 02 MAY 2007

     FILE 'HCAPLUS' ENTERED AT 16:18:06 ON 02 MAY 2007
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L23          857 S FOSCARNET
L24          121 S L23 AND L7
L25           93 S L24 AND 1800<=PY<=2003

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L31  ANSWER 1 OF 1  HCAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:         2001:580763  HCAPLUS <<LOGINID::20070502>>
DOCUMENT NUMBER:          135:327001
TITLE:                    The potency of acyclovir can be markedly different in
                          different cell types
AUTHOR(S):                Brandi, Giorgio; Schiavano, Giuditta F.; Balestra,
                          Emanuela; Tavazzi, Barbara; Perno, Carlo-Federico;
                          Magnani, Mauro
CORPORATE SOURCE:         Institute of Toxicologic Hygienic and Environmental
                          Science, "G. Fornaini" University of Urbino, Urbino,
                          Italy
SOURCE:                   Life Sciences (2001), 69(11), 1285-1290
                          CODEN: LIFSAK; ISSN: 0024-3205
PUBLISHER:                Elsevier Science Inc.
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB   Acyclovir is an acyclic guanine analog with a considerable activity
     against herpes simplex viruses.  We studied the antiherpetic
     activity of acyclovir in macrophages and fibroblast cell lines.  Utilizing
     a plaque reduction assay we found that acyclovir potently inhibited the HSV-1
     replication in macrophages (EC50 = 0.0025 μM) compared to Vero (EC50 =
     8.5 μM) and MRC-5 (EC50 = 3.3 μM) cells.  The cytotoxicity of
     acyclovir was not detected at concns. ≤ 20 μM, thus the
     selective index in macrophages was > 8000.  This marked difference in
     antiherpetic activity between macrophages and fibroblasts was not observed
     with Foscarnet and PMEA.  We suggest that this potent antiviral
     effect of acyclovir is mainly due to a proficient phosphorylation of the
     drug and/or a favorable dGTP/acyclovir triphosphate
     ratio in macrophage cells.
IT   59277-89-3, Acyclovir 106941-25-7, PMEA
     RL: BAC (Biological activity or effector, except adverse); BSU (Biological
     study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES
     (Uses)
        (potency of acyclovir can be markedly different in different cell
        types)
RN   59277-89-3  HCAPLUS
CN   6H-Purin-6-one, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]-  (CA
     INDEX NAME)
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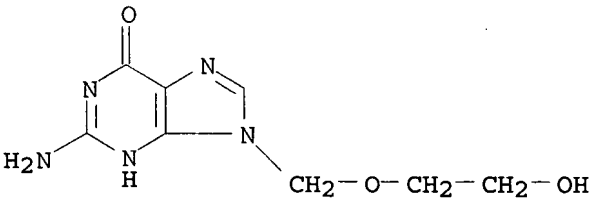

RN 106941-25-7 HCAPLUS
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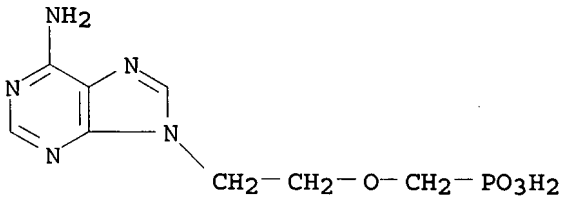

REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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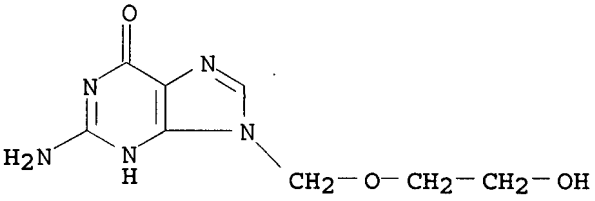
L28 ANSWER 1 OF 23 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:741595 HCAPLUS <<LOGINID::20070502>>
DOCUMENT NUMBER: 140:104511
TITLE: Comparison of HSV-1 thymidine kinase-dependent and -independent inhibition of replication-competent adenoviral vectors by a panel of drugs
AUTHOR(S): Wildner, Oliver; Hoffmann, Dennis; Jogler, Christian; Ueberla, Klaus
CORPORATE SOURCE: Bldg. MA, Abteilung fuer Molekulare und Medizinische Virologie, Ruhr-Universitaet Bochum, Bochum, D-44801, Germany
SOURCE: Cancer Gene Therapy (2003), 10(10), 791-802
CODEN: CGTHEG; ISSN: 0929-1903
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Replication-competent adenoviral vectors hold the promise to be more efficient gene delivery vehicles than their replication-deficient counterparts, but they are also associated with a higher risk for adverse effects, especially in light of the fact that there is no established effective therapy for serious, disseminated adenovirus infection. To assess whether the therapeutic options to inhibit adenoviral replication can be enhanced by expressing a suicide gene, we examined the antiadenoviral effects of 15 drugs against wild-type adenovirus type 5 (Ad5) and an Ad5-based replication-competent vector expressing herpes simplex virus-1 thymidine kinase (HSV-tk) (Ad.OW34) using a real-time polymerase chain reaction -based assay and flow cytometry. Ad5 and Ad.OW34 were highly susceptible to the fluorinated pyrimidine analogs 5-fluoro-2'-deoxyuridine (FUdR), 5-fluorouridine (FUR), and trifluorothymidine (TFT), with a mean 50% inhibitory concentration (IC50) ranging from 0.12 to 0.32 μM. The mean IC50 of ribavirin and cidofovir (CDV) for Ad5, the most frequently used drugs to treat adenovirus disease,

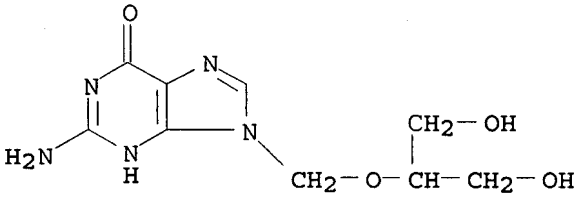
was 6.87 and 3.19 μM, resp. In contrast to Ad5, the Ad.OW34 vector was susceptible to (E)-5-(2-bromovinyl)-2'-deoxyuridine (BVdU, IC50 0.09 μM), ganciclovir (GCV, IC50 0.19 μM), and acyclovir (ACV, IC50 32.04 μM). Addnl., we demonstrated in an animal model that Ad.OW34 vector replication can be inhibited significantly by GCV, CDV, and TFT by 35.2, 7.7, and 3.7-fold, resp., compared to untreated animals. The observed antiadenoviral effects were primarily not through cell killing, since the in vitro 50% cytotoxic concns. (CC50) were more than 1000 times higher than the antiadenoviral IC50 of the drugs examined, even in cells stably expressing HSV-tk. Since for HSV-tk-dependent inhibition of adenoviral vectors, stability of HSV-tk expression is crucial, we examined Ad.OW34 vector stability, by passaging the vector 10 times serially in the presence of 10 μM GCV. The HSV-tk/GCV system neither changed the susceptibility of Ad.OW34 to GCV significantly nor detectable vector rearrangements occurred, suggesting that the system might be suitable as a fail-safe mechanism to stop adenoviral vector replication.

IT 59277-89-3, Acyclovir 82410-32-0, Ganciclovir
113852-37-2, Cidofovir
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of replication competent adenoviral vectors by a panel of drugs)

RN 59277-89-3 HCAPLUS
CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]- (CA INDEX NAME)

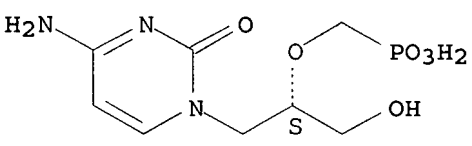


RN 82410-32-0 HCAPLUS
CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]- (CA INDEX NAME)



RN 113852-37-2 HCAPLUS
CN Phosphonic acid, P-[[(1S)-2-(4-amino-2-oxo-1(2H)-pyrimidinyl)-1-(hydroxymethyl)ethoxy]methyl]- (CA INDEX NAME)

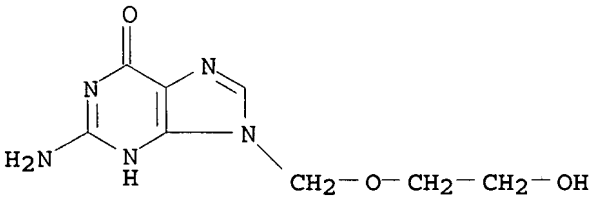
Absolute stereochemistry.



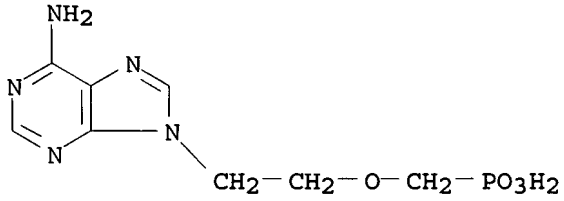
REFERENCE COUNT: 101 THERE ARE 101 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d l28 ibib abs hitstr 2-20

L28 ANSWER 2 OF 23 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:526763 HCAPLUS <<LOGINID::20070502>>
DOCUMENT NUMBER: 139:175724
TITLE: Drug resistance patterns of recombinant herpes simplex virus DNA polymerase mutants generated with a set of overlapping cosmids and plasmids
AUTHOR(S): Bestman-Smith, Julie; Boivin, Guy
CORPORATE SOURCE: Centre de Recherche en Infectiologie of the Centre Hospitalier Universitaire de Quebec (Pavillon CHUL) and Universite Laval, Quebec, Can.
SOURCE: Journal of Virology (2003), 77(14), 7820-7829
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Herpes simplex virus (HSV) DNA polymerase (Pol) mutations can confer resistance to all currently available antiherpetic drugs. However, discrimination between mutations responsible for drug resistance and those that are part of viral polymorphism can be difficult with current methodologies. A new system is reported for rapid generation of recombinant HSV type 1 (HSV-1) DNA Pol mutants based on transfection of a set of overlapping viral cosmids and plasmids. With this approach, twenty HSV-1 recombinants with single or dual mutations within the DNA pol gene were successfully generated and subsequently evaluated for their susceptibilities to acyclovir (ACV), foscarnet (FOS), cidofovir (CDV), and adefovir (ADV). Mutations within DNA Pol conserved regions II (A719T and S724N), VI (L778M, D780N, and L782I), and I (F891C) were shown to induce cross-resistance to ACV, FOS, and ADV, with two of these mutations (S724N and L778M) also conferring significant reduction in CDV susceptibility. Mutant F891C was associated with the highest levels of resistance towards ACV and FOS and was strongly impaired in its replication capacity. One mutation (D907V) lying outside of the conserved regions was also associated with this ACV-, FOS-, and ADV-resistant phenotype. Some mutations (K522E and Y577H) within the δ-region C were lethal, whereas others (P561S and V573M) induced no resistance to any of the drugs tested. Recombinants harboring mutations within conserved regions V (N961K) and VII (Y941H) were resistant to ACV but susceptible to FOS. Finally, mutations within conserved region III were associated with various susceptibility profiles. This new system allows a rapid and accurate evaluation of the functional role of various DNA Pol mutations, which should translate into improved management of drug-resistant HSV infections.
IT 59277-89-3, Acyclovir 106941-25-7, Adefovir 113852-37-2, Cidofovir
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(drug resistance patterns of recombinant herpes simplex virus DNA polymerase mutants generated with a set of overlapping cosmids and plasmids)
RN 59277-89-3 HCAPLUS
CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]- (CA INDEX NAME)

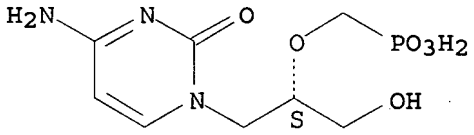


RN 106941-25-7 HCAPLUS
CN Phosphonic acid, P-[[2-(6-amino-9H-purin-9-yl)ethoxy]methyl]- (CA INDEX NAME)



RN 113852-37-2 HCAPLUS
CN Phosphonic acid, P-[[(1S)-2-(4-amino-2-oxo-1(2H)-pyrimidinyl)-1-(hydroxymethyl)ethoxy]methyl]- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

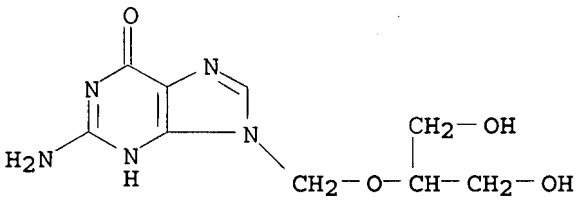
L28 ANSWER 3 OF 23 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:513247 HCAPLUS <<LOGINID::20070502>>
DOCUMENT NUMBER: 139:358071
TITLE: In vitro activities of benzimidazole D- and L-ribonucleosides against herpesviruses
AUTHOR(S): Williams, Stephanie L.; Hartline, Caroll B.; Kushner, Nicole L.; Harden, Emma A.; Bidanset, Deborah J.; Drach, John C.; Townsend, Leroy B.; Underwood, Mark R.; Biron, Karen K.; Kern, Earl R.
CORPORATE SOURCE: University of Alabama School of Medicine, Birmingham, AL, USA
SOURCE: Antimicrobial Agents and Chemotherapy (2003), 47(7), 2186-2192
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Herpes simplex virus types 1 and 2 (HSV-1 and HSV-2), varicella-zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), human herpesvirus 6 (HHV-6), and human herpesvirus 8 (HHV-8) are responsible for a number of clin. manifestations in both normal and

immunocompromised individuals. The parent benzimidazole ribonucleosides evaluated in this series, 2-bromo-5,6-dichloro-1-(β-D-ribofuranosyl)benzimidazole (BDCRB) and maribavir (1263W94), are potent and selective inhibitors of human CMV replication. These nucleosides act by two different mechanisms. BDCRB blocks the processing and maturation of viral DNA, whereas 1263W94 inhibits the viral enzyme pUL97 and interferes with DNA synthesis. In the present study, we have evaluated the in vitro antiviral activity of BDCRB, an analog, GW275175X (175X), and 1263W94 against the replication of HSV-1, HSV-2, VZV, CMV, EBV, HHV-6, and HHV-8. By using various methodologies, significant activity was observed against human CMV and EBV but not against HSV-1, HSV-2, VZV, HHV-6, or HHV-8. Plaque reduction assays performed on a variety of laboratory and clin. isolates of human CMV indicated that all strains, including those resistant to ganciclovir (GCV) and foscarnet, were sensitive to all three benzimidazole ribonucleosides, with mean 50% effective concentration values of about 1 to 5 μM compared to that of GCV at 6 μM. The toxicity of these compds. in tissue culture cells appeared to be similar to that observed with GCV. These results demonstrate that the benzimidazole ribonucleosides are active against human CMV and EBV and suggest that they may be useful for the treatment of infections caused by these herpesviruses.

IT 82410-32-0, Ganciclovir
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(-resistant strains; in vitro activities of benzimidazole D- and L-ribonucleosides against herpesviruses)

RN 82410-32-0 HCAPLUS

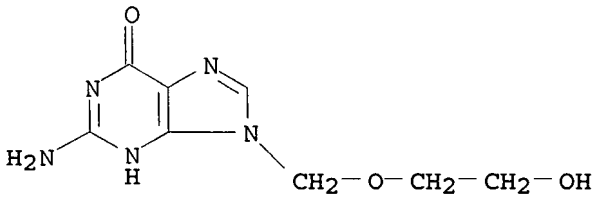
CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]- (CA INDEX NAME)



IT 59277-89-3, Acyclovir 113852-37-2, Cidofovir
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(comparison compound; in vitro activities of benzimidazole D- and L-ribonucleosides against herpesviruses)

RN 59277-89-3 HCAPLUS

CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]- (CA INDEX NAME)

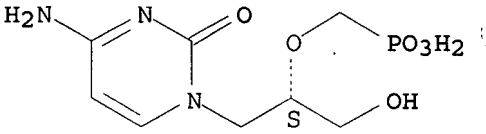


RN 113852-37-2 HCAPLUS

CN Phosphonic acid, P-[[(1S)-2-(4-amino-2-oxo-1(2H)-pyrimidinyl)-1-

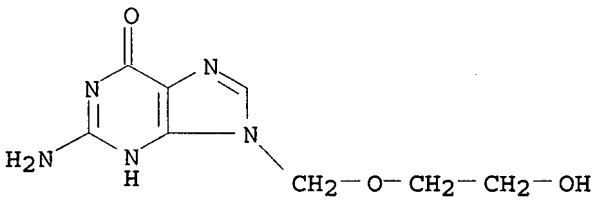
(hydroxymethyl)ethoxy]methyl]- (CA INDEX NAME)

Absolute stereochemistry.



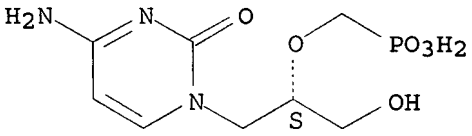
REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 4 OF 23 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:397332 HCAPLUS <<LOGINID::20070502>>
DOCUMENT NUMBER: 139:110942
TITLE: Management of acyclovir-resistant herpes simplex virus
AUTHOR(S): Chilukuri, Suneel; Rosen, Ted
CORPORATE SOURCE: Department of Dermatology, Baylor College of Medicine, Houston, TX, 77030, USA
SOURCE: Dermatologic Clinics (2003), 21(2), 311-320
CODEN: DRMCDJ; ISSN: 0733-8635
PUBLISHER: W. B. Saunders Co.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Acyclovir and related compds. are the mainstay of therapy of infections that are caused by human herpesvirus types I, II, and III. Resistance to this class of drugs has increased among patients who are immunocompromised (bone marrow and organ transplant patients, patients with cancer, and patients infected with HIV), leading to persistent mucocutaneous lesions or serious systemic infections. Alternative treatment regimens include parenteral foscarnet, vidarabine, and cidofovir, as well as topical foscarnet, cidofovir, trifluridine, and imiquimod. Ribonucleotide reductase inhibitors offer considerable promise for future treatment.
IT 59277-89-3, Acyclovir 113852-37-2, Cidofovir
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(management of acyclovir-resistant herpes simplex virus)
RN 59277-89-3 HCAPLUS
CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]- (CA INDEX NAME)



RN 113852-37-2 HCAPLUS
CN Phosphonic acid, P-[[(1S)-2-(4-amino-2-oxo-1(2H)-pyrimidinyl)-1-(hydroxymethyl)ethoxy]methyl]- (CA INDEX NAME)

Absolute stereochemistry.

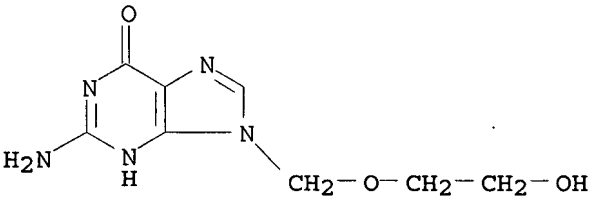


REFERENCE COUNT: 122 THERE ARE 122 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 5 OF 23 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:102544 HCAPLUS <<LOGINID::20070502>>
DOCUMENT NUMBER: 139:269931
TITLE: Herpes simplex virus resistance to antiviral drugs
AUTHOR(S): Morfin, Florence; Thouvenot, Danielle
CORPORATE SOURCE: 8 avenue Rockefeller, Domaine Rockefeller, Laboratory of Virology of the Hospices Civils de Lyon, Lyon, 69373, Fr.
SOURCE: Journal of Clinical Virology (2003), 26(1), 29-37
CODEN: JCVIFB; ISSN: 1386-6532
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Herpes simplex virus (HSV) infections are efficiently treated with antiviral drugs such as acyclovir (ACV). However, resistance has been reported, mainly among immunocompromised patients (prevalence around 5%) and particularly allogeneic bone marrow transplant patients (prevalence reaching 30%). Resistance to ACV is associated with mutations on one of the two viral enzymes involved in the ACV mechanism of action: thymidine kinase (TK) and DNA polymerase. In 95% of the cases, ACV resistance is associated with a mutation in the TK gene as this enzyme is not essential for viral replication, unlike viral DNA polymerase, which is rarely involved in resistance. Strains resistant to ACV are almost always cross-resistant to other TK-dependent drugs such as penciclovir and famciclovir. Resistant infections can be managed by foscarnet or cidofovir but both are more toxic than ACV. These drugs also inhibit viral DNA polymerase but they are active on most ACV-resistant HSV as they do not depend on TK; nevertheless virus resistant to ACV because of a mutation in the DNA polymerase may be cross-resistant to these mols. Published data on genetic characterization of resistant clin. isolates point out hot spots in viral TK and DNA polymerase genes. TK mutations associated with resistance are either insertion or deletion (codons 92 and 146 of TK gene) or substitution (codon 176-177, 336 of TK gene). DNA polymerase mutations are mainly located in conserved sites of the enzyme. A high level of gene polymorphism has also been reported for these genes, especially for TK. These results are useful for the development of rapid genotypic assays for the detection of mutations associated with resistance.

IT 59277-89-3, Acyclovir
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(herpes simplex virus resistance to antiviral drugs)
RN 59277-89-3 HCAPLUS
CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]- (CA INDEX NAME)



REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 6 OF 23 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:22872 HCAPLUS <<LOGINID::20070502>>
DOCUMENT NUMBER: 138:89816
TITLE: Preparation of pyridine ring-containing benzoxazinone derivatives for treatment of viral infections
INVENTOR(S): Takahashi, Wataru; Watanabe, Naoto; Saito, Yasuyoshi
PATENT ASSIGNEE(S): Asahi Kasei Kabushiki Kaisha, Japan
SOURCE: PCT Int. Appl., 104 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003002558	A1	20030109	WO 2002-JP5795	20020611 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
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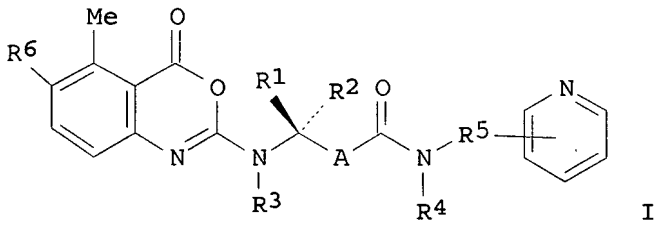
EP 1403269	A1	20040331	EP 2002-733468	20020611
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2004116420	A1	20040617	US 2003-480451	20031212
PRIORITY APPLN. INFO.:			JP 2001-179282 A	20010613
			JP 2001-379282 A	20011212
			WO 2002-JP5795 W	20020611

OTHER SOURCE(S): MARPAT 138:89816
GI

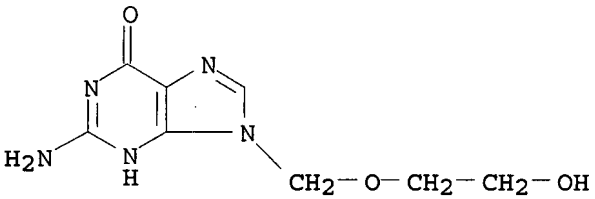


I

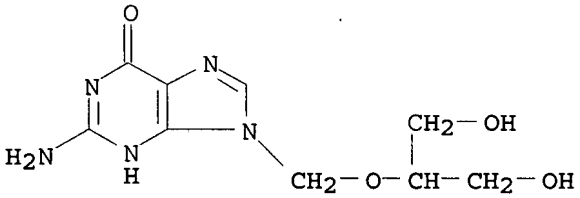
AB The title compds. I [R1, R2 = H, alkyl, etc.; or R1CR2 = cycloalkyl; A = (CH2)n; n = 0 or 1; R3 = H, alkyl, etc.; R4 = H, alkyl, alkenyl, etc.; R5 = alkylene; or NR4R5 = heterocyclyl; R6 = H, halo, etc.] are prepared I have excellent protease inhibitory activity. I are useful in the treatment of viral infectious diseases, in particular herpesvirus infections. Compds. of this invention in vitro showed EC90 values of 3.2 μM to > 12 μM against HSV-1.

IT 59277-89-3, Aciclovir 82410-32-0, Ganciclovir
104227-87-4, Famciclovir 113852-37-2, Cidofovir
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination of antiviral pyridine ring-containing benzoxazinone derivs. and another antiviral agent)

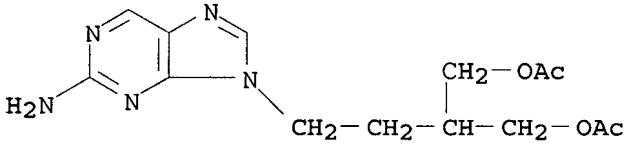
RN 59277-89-3 HCAPLUS
CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]- (CA INDEX NAME)



RN 82410-32-0 HCAPLUS
CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]- (CA INDEX NAME)

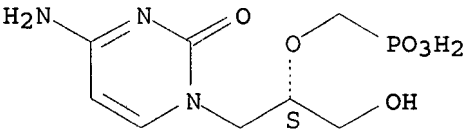


RN 104227-87-4 HCAPLUS
CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-, 1,3-diacetate (CA INDEX NAME)



RN 113852-37-2 HCAPLUS
CN Phosphonic acid, P-[[(1S)-2-(4-amino-2-oxo-1(2H)-pyrimidinyl)-1-(hydroxymethyl)ethoxy]methyl]- (CA INDEX NAME)

Absolute stereochemistry.

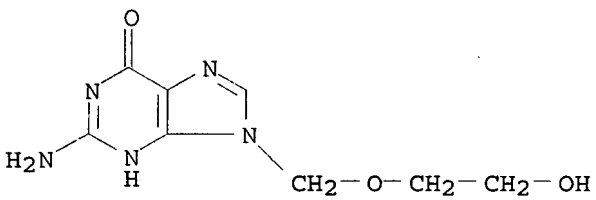


REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 7 OF 23 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:822158 HCAPLUS <<LOGINID::20070502>>
DOCUMENT NUMBER: 138:183762
TITLE: Genotypic and phenotypic characterization of the thymidine kinase of ACV-resistant HSV-1 derived from an acyclovir-sensitive herpes simplex virus type 1 strain
AUTHOR(S): Saijo, Masayuki; Suzutani, Tatsuo; De Clercq, Erik; Niikura, Masahiro; Maeda, Akihiko; Morikawa, Shigeru; Kurane, Ichiro
CORPORATE SOURCE: Department of Virology 1, Special Pathogens Laboratory, National Institute of Infectious Diseases, Musashimurayama, Tokyo, 208-0011, Japan
SOURCE: Antiviral Research (2002), 56(3), 253-262
CODEN: ARSRDR; ISSN: 0166-3542
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

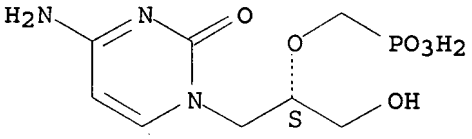
AB Twenty-four strains of acyclovir (ACV)-resistant (ACVr) herpes simplex virus type 1 (HSV-1) were generated from the HSV-1 TAS strain by exposure to ACV, and the genotype and phenotype of the thymidine kinase (TK) from these mutants were analyzed. The TK polypeptide of the ACVr HSV-1 strains was examined by Western blot using an anti-HSV-1 TK rabbit serum. The sensitivity of each strain to ACV, foscarnet and cidofovir (CDV) was also determined A single guanine (G) insertion or a single cytosine (C) deletion was detected in 12 of the 24 ACVr strains at the G or C homopolymer stretches within the TK gene. Genotypic anal. predicted that two thirds of the ACVr HSV-1 strains expressed truncated TK polypeptides, while one third expressed viral TK polypeptide with a single amino acid substitution at various sites. Western blot abnormalities in the viral TK polypeptides were identified in 21 ACVr strains. There was an inverse correlation between the susceptibility of the HSV-1 mutant strains to ACV and that to CDV. Nucleotide sequencing of the TK gene and Western blot anal. of the viral TK polypeptides are considered to be one of the methods for predicting virus sensitivity to ACV and CDV.

IT 59277-89-3, Acyclovir
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(ACV; genotypic and phenotypic characterization of thymidine kinase of acyclovir-resistant herpes simplex virus derived from acyclovir-sensitive HSV-1 strain)
RN 59277-89-3 HCAPLUS
CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]- (CA INDEX NAME)



IT 113852-37-2, Cidofovir
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(CDV, correlation between susceptibility of HSV-1 mutant strains to ACV and; genotypic and phenotypic characterization of thymidine kinase of acyclovir-resistant herpes simplex virus derived from acyclovir-sensitive HSV-1 strain)
RN 113852-37-2 HCAPLUS
CN Phosphonic acid, P-[[(1S)-2-(4-amino-2-oxo-1(2H)-pyrimidinyl)-1-(hydroxymethyl)ethoxy]methyl]- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 8 OF 23 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:72315 HCAPLUS <<LOGINID::20070502>>
DOCUMENT NUMBER: 136:129036
TITLE: Method of screening 4-hydroxyquinolin (4-HQ), 4-oxo-dihydroquinoline (4-oxo-DHQ), and 4-oxo-dihydrothienopyridine (4-oxo-DHTP) derivatives as non-nucleoside herpesvirus DNA polymerase inhibitor
INVENTOR(S): Homa, Fred L.; Wathen, Michael W.; Hopkins, Todd A.; Thomsen, Darrel R.
PATENT ASSIGNEE(S): Pharmacia & Upjohn Company, USA
SOURCE: PCT Int. Appl., 126 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

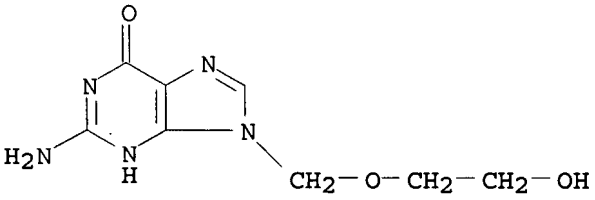
PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2002006513	A2	20020124	WO 2001-US16525		20010713 <--
WO 2002006513	A3	20030123			
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
US 2002076789	A1	20020620	US 2001-904065		20010712 <--
US 6682892	B2	20040127			
AU 2001072920	A5	20020130	AU 2001-72920		20010713 <--
US 2004115623	A1	20040617	US 2003-692556		20031024
PRIORITY APPLN. INFO.:			US 2000-218118P	P	20000713
			US 2001-283880P	P	20010413
			US 2001-904065	A3	20010712
			WO 2001-US16525	W	20010713

AB The present invention provides a method for selecting non-nucleoside

herpesvirus DNA polymerase inhibitors from 4-HQ, 4-oxo-DHQ, and 4-oxo-DHTP derivs. by measuring IC50. The invention also provides sequences of mutant herpesvirus DNA polymerase genes which resist non-nucleoside inhibitors, and herpesvirus mutant strains containing the drug-resistant DNA polymerase genes. The present invention relates to a method for selecting an anti-herpes viral compound and a method for selectively inhibiting herpesvirus in a human host in need of such treatment. The present invention relates to a method for selecting an anti-herpes viral compound and a method for selectively inhibiting herpesvirus in a human host in need of such treatment.

IT 59277-89-3, Acyclovir 82410-32-0, Ganciclovir
113852-37-2, Cidofovir
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(4-HQ,4-oxo-DHQ, and 4-oxo-DHTP derivs. as non-nucleoside herpesvirus DNA polymerase inhibitor)

RN 59277-89-3 HCAPLUS
CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]- (CA INDEX NAME)



RN 82410-32-0 HCAPLUS
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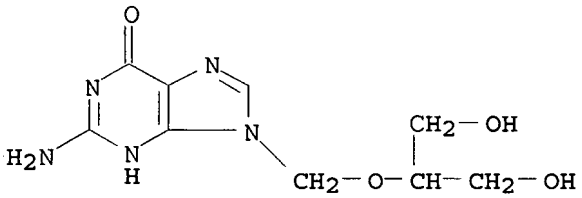
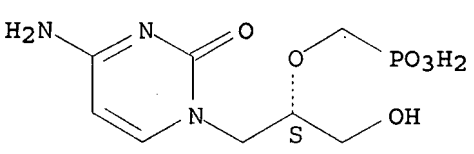


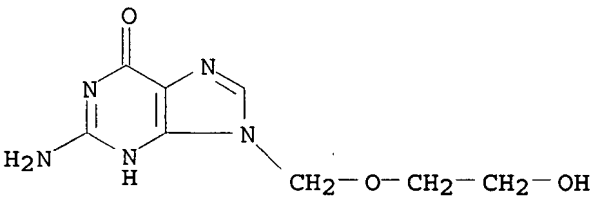
RN 113852-37-2 HCAPLUS
CN Phosphonic acid, P-[[(1S)-2-(4-amino-2-oxo-1(2H)-pyrimidinyl)-1-(hydroxymethyl)ethoxy]methyl]- (CA INDEX NAME)

Absolute stereochemistry.



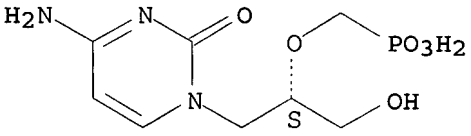
L28 ANSWER 9 OF 23 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:825249 HCAPLUS <<LOGINID::20070502>>

DOCUMENT NUMBER: 136:318855
TITLE: Infection due to aciclovir resistant herpes simplex virus in patients undergoing allogeneic hematopoietic stem cell transplantation
AUTHOR(S): Venard, V.; Dauendorffer, J. N.; Carret, A. S.; Corsaro, D.; Edert, D.; Bordigoni, P.; Le Faou, A.
CORPORATE SOURCE: Unite mixte de recherche 7565 UHP-CNRS, laboratoire de bacteriologie-virologie, faculte de medecine, Vandoeuvre-les-Nancy, Fr.
SOURCE: Pathologie Biologie (2001), 49(7), 553-558
CODEN: PTBIAN; ISSN: 0031-3009
PUBLISHER: Editions Scientifiques et Medicales Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Over an 8-mo period from Oct. 1997 to May 1998, 4 patients who had received bone marrow transplant (BMT) from unrelated donor presented with severe mucosal cutaneous infections involving aciclovir resistant herpes simplex virus 1 (HSV-1). The 4 isolates were aciclovir (ACV) resistant, 3 of which were also foscarnet resistant as determined by the dye uptake method. The sequencing of the thymidine kinase (TK) gene did not permit to establish a relation between mutations and resistance to ACV. 3 Patients were considered as clin. cured of their HSV infection by replacement of ACV or foscarnet with either valaciclovir (1 case) or cidofovir (two cases) but eventually 2 of them died of graft vs host disease. 1 Patient died of extensive HSV infection despite administration of cidofovir. This study emphasizes the importance of monitoring the herpes virus resistance to antiviral drugs in bone marrow transplant recipients and the usefulness of the evaluation of novel antiviral drug for treatment of infections due to strains of HSV resistant to ACV and foscarnet that occur in about 5% of immunocompromised patients.
IT 59277-89-3, Aciclovir
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aciclovir resistant herpes simplex virus infection in patients undergoing allogeneic hematopoietic stem cell transplantation)
RN 59277-89-3 HCAPLUS
CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]- (CA INDEX NAME)



IT 113852-37-2, Cidofovir
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiviral therapy of aciclovir resistant HSV infection in patients undergoing allogeneic hematopoietic stem cell transplantation)
RN 113852-37-2 HCAPLUS
CN Phosphonic acid, P-[[(1S)-2-(4-amino-2-oxo-1(2H)-pyrimidinyl)-1-(hydroxymethyl)ethoxy]methyl]- (CA INDEX NAME)

Absolute stereochemistry.



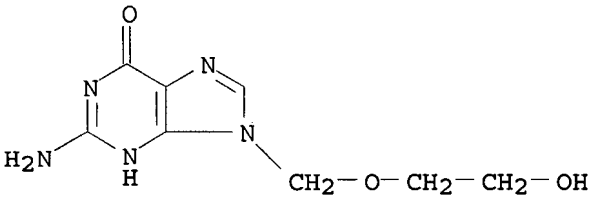
REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 10 OF 23 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:223450 HCAPLUS <<LOGINID::20070502>>
DOCUMENT NUMBER: 135:174514
TITLE: Prophylaxis against herpesvirus infections in transplant recipients
AUTHOR(S): Ljungman, Per
CORPORATE SOURCE: Department of Haematology, Karolinska Institutet, Huddinge University Hospital, Huddinge, Swed.
SOURCE: Drugs (2001), 61(2), 187-196
CODEN: DRUGAY; ISSN: 0012-6667
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 63 refs. Herpesvirus infections are important after stem cell and organ transplant. During the last decades several antiviral agents have been introduced with efficacy against herpesviruses. These agents are the nucleoside analogs acyclovir, valaciclovir, famciclovir, and ganciclovir; the nucleotide analog cidofovir; and the pyrophosphate analog foscarnet. Several studies have been performed with antiviral agents with the aim to reduce morbidity and mortality associated with herpesvirus infections in transplant recipients. Aciclovir and valaciclovir have been examined in randomized, controlled trials in both solid organ and stem cell transplant patients, and were shown to be very effective for the prevention of herpes simplex virus (HSV) and varicella-zoster virus infections. In addition, these drugs were shown to reduce cytomegalovirus (CMV) infection and improve survival in allogenic stem cell transplant patients and to reduce CMV infection, CMV disease (aciclovir and valaciclovir), and acute rejection (valaciclovir) in renal transplant patients. Ganciclovir is very effective for the prevention of CMV infection and disease in both stem cell and solid organ transplant recipients. It can also be used in preemptive strategies in which the aim is to prevent CMV disease in patients who have ongoing CMV infection documented by antigenemia or detection of CMV DNA. The latter strategy has the advantage of reducing the exposure to the drug and thereby the risk for toxicity. Foscarnet has also been shown to be effective as preemptive therapy for CMV in allogenic stem cell transplant patients and as therapy for aciclovir-resistant HSV infections. Finally cidofovir is an interesting agent with broad spectrum antiherpes virus efficacy. However, because of the drug's toxicity profile, further studies are needed.

IT 59277-89-3, Aciclovir 82410-32-0, Ganciclovir 104227-87-4, Famciclovir 113852-37-2, Cidofovir
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prophylaxis against herpesvirus infections in transplant recipients)

RN 59277-89-3 HCAPLUS
CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]- (CA INDEX NAME)



RN 82410-32-0 HCAPLUS
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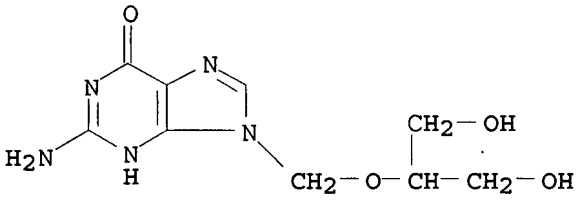
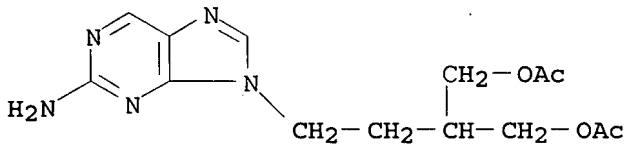
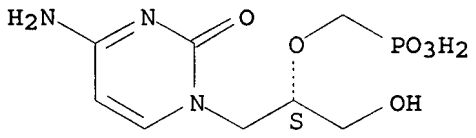


RN 104227-87-4 HCAPLUS
CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-, 1,3-diacetate (CA INDEX NAME)



RN 113852-37-2 HCAPLUS
CN Phosphonic acid, P-[[(1S)-2-(4-amino-2-oxo-1(2H)-pyrimidinyl)-1-(hydroxymethyl)ethoxy]methyl]- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 11 OF 23 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:41285 HCAPLUS <<LOGINID::20070502>>
DOCUMENT NUMBER: 135:116203
TITLE: Current recommendations for the treatment of genital herpes
AUTHOR(S): Leung, Daniel T.; Sacks, Stephen L.
CORPORATE SOURCE: Wake Forest University School of Medicine, Winston Salem, NC, USA

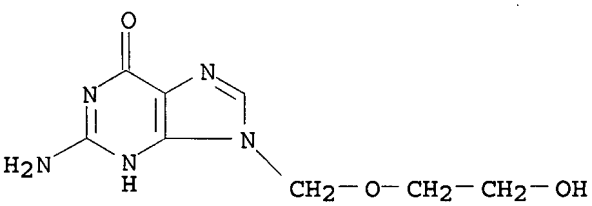
SOURCE: Drugs (2000), 60(6), 1329-1352
CODEN: DRUGAY; ISSN: 0012-6667
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 228 refs. The incidence of genital herpes continues to increase in epidemic-like fashion. Aciclovir (acyclovir) has been the original gold standard of therapy. The recent addition of famciclovir and valaciclovir as antiherpes drugs has improved convenience as well as the efficacy of treatment. Although aciclovir remains a widely prescribed and reliable drug, its administration schedule falls short of the ease of usage that the newer nucleoside analogs offer, for both episodic and suppressive therapy. Suppression of symptomatic disease and asymptomatic shedding from the genitalia have both become popular approaches, if not the primary targets of antiviral therapy. Knowing that asymptomatic disease leads to most cases of transmission strongly suggests that suppression with antiviral agents could reduce transmission risk in discordant couples. Unfortunately, the role for antivirals in reducing transmission remains to be proven in clin. trials. Neonatal herpes is now successfully treated using aciclovir. Current randomized clin. trials are examining aciclovir and valaciclovir administration, as well as safety and efficacy for post-acute suppressive therapy. Prevention of recurrences in pregnancy is also a topic under investigation, with a view to reducing the medical need for Cesarean section, or alternatively (and far less likely to be accomplished) to protect the neonate. Although resistance is largely limited to the immunocompromised and a change in resistance patterns is not expected, several drugs are available for the treatment of aciclovir-resistant strains of herpes simplex. Foscarnet is the main alternative with proven efficacy in this setting. Unfortunately, administration of foscarnet requires i.v. therapy, although a single anecdote of topical foscarnet efficacy in this setting has been published. Alternatives include cidofovir gel, which is not com. available but can be formulated locally from the i.v. preparation Less effective alternatives include trifluridine and interferon. Future possibilities for treatment of genital herpes include a microparticle-based controlled-release formulation of aciclovir and resiquimod (VML-600; R-848). The search for an effective therapeutic vaccine for genital herpes has not been successful to date, although a live virus glycoprotein H-deficient (DISC) vaccine is currently in clin. trials. Recent data suggest that seroneg. women are protected (albeit, not fully) by a glycoprotein D recombinant vaccine with adjuvant. Despite the established safety and convenience of current treatment options, better suppressive options and topical treatment options are much needed. Studies using existing agents as potential tools to avoid Cesarean section, or transmission to neonate or partner are ongoing. Both vaccines and antivirals may eventually play a role in prevention of infection.

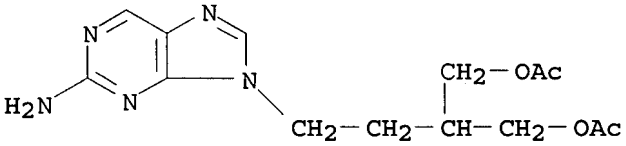
IT 59277-89-3, Aciclovir 104227-87-4, Famciclovir
113852-37-2, Cidofovir
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(current recommendations for treatment of genital herpes in humans)

RN 59277-89-3 HCAPLUS

CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]- (CA INDEX NAME)

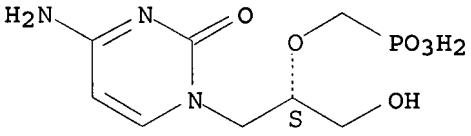


RN 104227-87-4 HCAPLUS
CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-, 1,3-diacetate (CA INDEX NAME)



RN 113852-37-2 HCAPLUS
CN Phosphonic acid, P-[[(1S)-2-(4-amino-2-oxo-1(2H)-pyrimidinyl)-1-(hydroxymethyl)ethoxy]methyl]- (CA INDEX NAME)

Absolute stereochemistry.



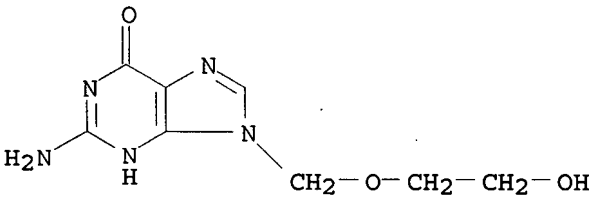
REFERENCE COUNT: 228 THERE ARE 228 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 12 OF 23 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:504602 HCAPLUS <<LOGINID::20070502>>
DOCUMENT NUMBER: 133:232393
TITLE: Resistance to antiviral drugs in herpes simplex virus infections among allogeneic stem cell transplant recipients: risk factors and prognostic significance
AUTHOR(S): Chakrabarti, Suparno; Pillay, Deenan; Ratcliffe, Daina; Cane, Patricia A.; Collingham, Kathryn E.; Milligan, Donald W.
CORPORATE SOURCE: Department of Haematology, University of Birmingham Medical School, Birmingham, B9 5SS, UK
SOURCE: Journal of Infectious Diseases (2000), 181(6), 2055-2058
CODEN: JIDIAQ; ISSN: 0022-1899
PUBLISHER: University of Chicago Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Herpes simplex virus (HSV) infections in 75 allogeneic stem cell transplant recipients were analyzed. Sixteen patients developed HSV disease following transplantation. The risk factors were age, sex (females), unrelated donor graft, and graft-vs.-host disease (GVHD) grade

≥2. Seven patients did not respond to acyclovir, and 3 patients failed to respond to foscarnet. Isolates from 4 patients developed resistance to acyclovir/penciclovir, and 3 patients had foscarnet-resistant isolates. The remaining 3 patients failed to respond to acyclovir, despite having sensitive isolates. All the isolates were sensitive to cidofovir, for which the IC50 values correlated inversely with those for acyclovir (P = .01). The risk factors for clin. resistance to antiviral drugs were a GVHD grade ≥2 (P = .001) and the lack of ganciclovir prophylaxis (P = .01), with a higher nonrelapse mortality in the latter group (P < .0001). Clin. as well as in vitro resistance to antiviral drugs is common in patients with severe GVHD and is associated with a poor outcome.

IT 59277-89-3, Acyclovir 82410-32-0, Ganciclovir
113852-37-2, Cidofovir
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(resistance to antiviral drugs in herpes simplex virus infections among allogeneic stem cell transplant recipients)

RN 59277-89-3 HCAPLUS
CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]- (CA INDEX NAME)



RN 82410-32-0 HCAPLUS
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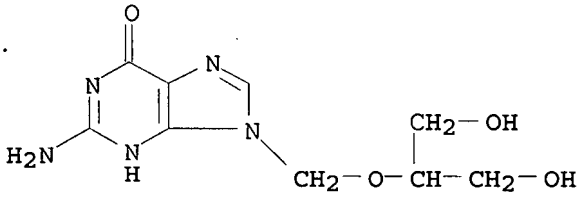
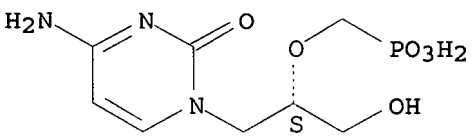


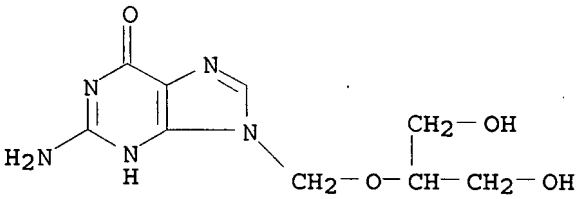
RN 113852-37-2 HCAPLUS
CN Phosphonic acid, P-[[(1S)-2-(4-amino-2-oxo-1(2H)-pyrimidinyl)-1-(hydroxymethyl)ethoxy]methyl]- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

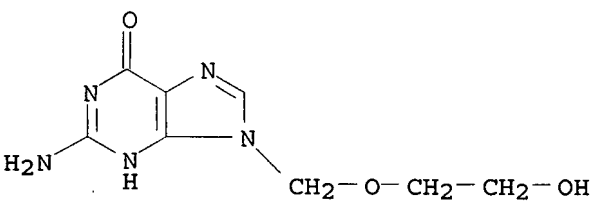
L28 ANSWER 13 OF 23 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:255804 HCAPLUS <<LOGINID::20070502>>
DOCUMENT NUMBER: 133:83919
TITLE: Antiviral activity of ganciclovir elaidic acid ester against herpesviruses
AUTHOR(S): Andrei, G.; Snoeck, R.; Neyts, J.; Sandvold, M. L.; Myhren, F.; De Clercq, E.
CORPORATE SOURCE: K.U. Leuven, Rega Institute for Medical Research, Louvain, B-3000, Belg.
SOURCE: Antiviral Research (2000), 45(3), 157-167
CODEN: ARSRDR; ISSN: 0166-3542
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A fatty acid derivative of ganciclovir (GCV), elaidic acid ganciclovir (E-GCV), has been evaluated for its inhibitory activity against laboratory and clin. strains of herpes simplex type 1 (HSV-1) and type 2 (HSV-2), varicella-zoster virus (VZV) and human cytomegalovirus (HCMV) in human embryonic lung fibroblasts. GCV, cidofovir, acyclovir (ACV), brivudin (BVDU) and foscarnet (PFA) were included as reference compds. The viruses studied were wild-type, thymidine kinase-deficient (TK-) and PFA-resistant (PFAr) HSV strains. The IC50 values obtained for E-GCV were 5- to 30-fold lower than those observed for GCV, the IC50 value of E-GCV for HSV-1 strain KOS being 0.07 nM. A similarly increased activity of E-GCV (as compared to GCV) was noted for TK- and PFAr HSV-1 or HSV-2 strains. However, E-GCV did not exhibit superior activity over GCV to VZV or HCMV in vitro. The antiviral efficacy of E-GCV was also evaluated in vivo against intracerebral HSV-2 infection in NMRI mice. Animals were treated i.p. or perorally with E-GCV, GCV or placebo once daily for 10 days, starting the day of infection. E-GCV compared to GCV at equimolar doses, proved markedly more efficacious than GCV in terms of reduction of mortality rate and delay of mean time of death. The elaidic acid ester of GCV should therefore be considered as a novel approach towards the treatment of HSV infections.
IT 82410-32-0, Ganciclovir
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiviral activity of ganciclovir elaidic acid ester against herpesviruses)
RN 82410-32-0 HCAPLUS
CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]- (CA INDEX NAME)



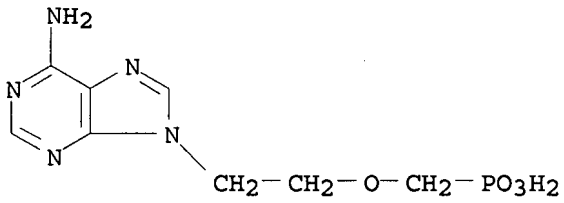
REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 14 OF 23 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:161933 HCAPLUS <<LOGINID::20070502>>

DOCUMENT NUMBER: 132:303023
TITLE: Resistance of herpes simplex virus type 1 against different phosphonylmethoxyalkyl derivatives of purines and pyrimidines due to specific mutations in the viral DNA polymerase gene
AUTHOR(S): Andrei, Graciela; Snoeck, Robert; De Clercq, Erik; Esnouf, Robert; Fiten, Pierre; Opdenakker, Ghislain
CORPORATE SOURCE: Laboratory of Antiviral Chemotherapy, Rega Institute for Medical Research, Katholieke Universiteit Leuven, Louvain, B-3000, Belg.
SOURCE: Journal of General Virology (2000), 81(3), 639-648
CODEN: JGVIAY; ISSN: 0022-1317
PUBLISHER: Society for General Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Drug-resistant strains of herpes simplex virus type 1 (HSV-1) were selected under the pressure of (S)-3-hydroxy-2-phosphonylmethoxypropyl (HPMP) derivs. of cytosine (HPMPC, cidofovir) and adenine (HPMPA) and 2-phosphonylmethoxyethyl (PME) derivs. of adenine (PMEA, adefovir) and 2,6-diaminopurine (PMEDAP). HPMPC-resistant (HPMPCr) and HPMPAr strains were cross-resistant to one another, but they remained sensitive to foscarnet (PFA), acyclovir (ACV) and the PME derivs., while the PMEAr and PMEDAPr strains showed cross-resistance to PFA and ACV. The PMEAr, PMEDAPr and PFAr mutants all revealed a single nucleotide change resulting in a Ser-724 to Asn mutation within the conserved region II of the DNA polymerase. Two HPMPAr clones and one HPMPCr clone possessed single amino acid changes in the DNA polymerase (HPMPAr clone D1, Leu-1007 to Met; HPMPAr clone B5, Ile-1028 to Thr; HPMPCr clone C3, Val-573 to Met). The HPMPCr clone A4 contained two mutations, Ala-136 to Thr and Arg-700 to Met. The mutation at position 136, located outside the catalytic domain of the enzyme, was not detected in other HPMPCr clones, suggesting that this mutation may not be responsible for the resistant phenotype. Residue 573 is located within the 3' → 5' exonuclease editing domain close to the catalytically important residues Tyr-577 and Asp-581. Similarly, residue 700 is located in the palm subdomain of the catalytic domain, adjacent to the Asp residues 717, 886 and 888 that are vital for polymerase activity. The HPMPAr mutations at residues 1007 and 1028, beyond the last conserved region, still fall within the thumb subdomain of the catalytic domain. The different drug-resistant mutants varied in neurovirulent behavior, the HPMPCr strains showing reduced neurovirulence compared with the wild-type.
IT 59277-89-3, Acyclovir 106941-25-7, Adefovir
113852-37-2, Cidofovir
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(resistance of herpes simplex virus type 1 against different phosphonylmethoxyalkyl derivs. of purines and pyrimidines due to specific mutations in viral DNA polymerase gene)
RN 59277-89-3 HCAPLUS
CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]- (CA INDEX NAME)

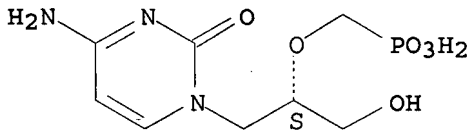


RN 106941-25-7 HCAPLUS
CN Phosphonic acid, P-[[2-(6-amino-9H-purin-9-yl)ethoxy]methyl]- (CA INDEX NAME)



RN 113852-37-2 HCAPLUS
CN Phosphonic acid, P-[[(1S)-2-(4-amino-2-oxo-1(2H)-pyrimidinyl)-1-(hydroxymethyl)ethoxy]methyl]- (CA INDEX NAME)

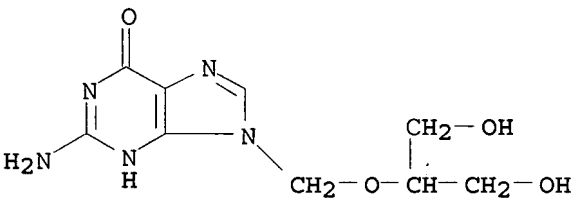
Absolute stereochemistry.



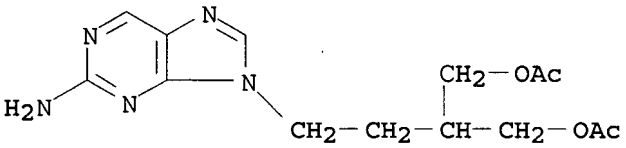
REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 15 OF 23 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:13232 HCAPLUS <<LOGINID::20070502>>
DOCUMENT NUMBER: 132:216381
TITLE: Advances in the research on new antiherpesvirus drugs
AUTHOR(S): Rostkowska-Nadolska, Beata
CORPORATE SOURCE: Katedra i Klinika Otolaryngologii, Akademia Medyczna, Wroclaw, 51685, Pol.
SOURCE: Postepy Higieny i Medycyny Doswiadczalnej (1999), 53(5), 675-687
CODEN: PHMDAD; ISSN: 0032-5449
PUBLISHER: Wydawnictwo Continuo
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Polish
AB A review with 31 refs. Significant advances have been made in the development of effective antiherpesvirus chemotherapy in recent decades. Acyclovir was approved for the treatment of herpes simplex virus infections over 15 yr ago and it remains an important and reliable antiviral agent. The most promising new antiviral drugs are described, including purine nucleoside analogs (vidarabine, penciclovir, famciclovir, ganciclovir, valaciclovir, lobucavir), pyrimidine nucleotide analogs (epervudine, sorivudine, cidofovir), Na foscarnet, docosanol, and vratizoline (denotivir). Focus is on drugs that have just entered the therapeutic use or are under clin. investigation and may become available shortly. The antiviral activity, results of clin. trials, and adverse side-effects are discussed.
IT 82410-32-0, Ganciclovir 104227-87-4, Famciclovir 113852-37-2, Cidofovir
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(virucides against herpes virus infections and recent research advances)

RN 82410-32-0 HCAPLUS
CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]- (CA INDEX NAME)

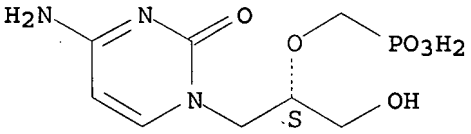


RN 104227-87-4 HCAPLUS
CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-, 1,3-diacetate (CA INDEX NAME)



RN 113852-37-2 HCAPLUS
CN Phosphonic acid, P-[[(1S)-2-(4-amino-2-oxo-1(2H)-pyrimidinyl)-1-(hydroxymethyl)ethoxy]methyl]- (CA INDEX NAME)

Absolute stereochemistry.

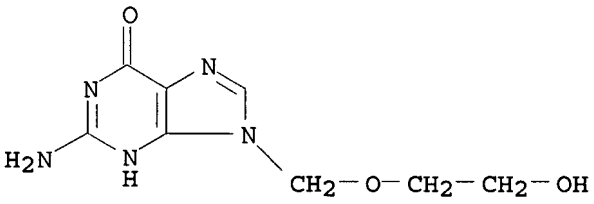


L28 ANSWER 16 OF 23 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:528343 HCAPLUS <<LOGINID::20070502>>
DOCUMENT NUMBER: 132:87784
TITLE: Characterization of the DNA polymerase and thymidine kinase genes of herpes simplex virus isolates from AIDS patients in whom acyclovir and foscarnet therapy sequentially failed
AUTHOR(S): Schmit, Isabelle; Boivin, Guy
CORPORATE SOURCE: Infectious Disease Research Center, Centre Hospitalier de l'Universite Laval, Quebec City, QC, Can.
SOURCE: Journal of Infectious Diseases (1999), 180(2), 487-490
CODEN: JIDIAQ; ISSN: 0022-1899
PUBLISHER: University of Chicago Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Herpes simplex virus (HSV) isolates were characterized from 8 AIDS patients in whom acyclovir and foscarnet therapy sequentially failed. The 6 postacyclovir (prefoscarnet) HSV isolates were resistant to acyclovir and susceptible to foscarnet. Of the 9

postfoscarnet isolates, 8 were foscarnet-resistant and acyclovir-susceptible, 1 was resistant to both drugs. Acycloviror foscarnet-resistant isolates retained susceptibility to cidofovir. The acyclovir-resistant isolates contained single-base substitutions or frameshift mutations in G or C homopolymer nucleotide repeats of the thymidine kinase gene. In contrast, the foscarnet -resistant strains contained single-base substitutions in conserved (II, III, or VI) or, more rarely, nonconserved (between I and VII) regions of the DNA polymerase (pol) gene. The single isolate exhibiting resistance to acyclovir and foscarnet contained mutations in both genes. In this study of clin. HSV isolates, DNA pol mutations conferring foscarnet resistance were not associated with decreased acyclovir or cidofovir susceptibility.

IT 59277-89-3, Acyclovir
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(phenotypic and genotypic anal. of foscarnet-resistant herpes simplex virus isolates from humans with AIDS resistant to acyclovir and foscarnet)

RN 59277-89-3 HCAPLUS
CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]- (CA INDEX NAME)



REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 17 OF 23 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:180764 HCAPLUS <<LOGINID::20070502>>
DOCUMENT NUMBER: 128:248590
TITLE: Topical antiviral compositions
INVENTOR(S): Ludwig, John
PATENT ASSIGNEE(S): Glaxo Group Ltd., UK; Ludwig, John
SOURCE: PCT Int. Appl., 16 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

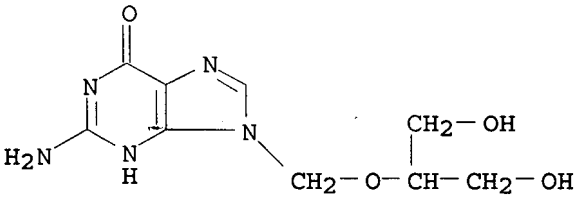
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9810768	A1	19980319	WO 1997-EP4945	19970910 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9743842	A	19980402	AU 1997-43842	19970910 <--

PRIORITY APPLN. INFO.: GB 1996-18974 A 19960911
WO 1997-EP4945 W 19970910

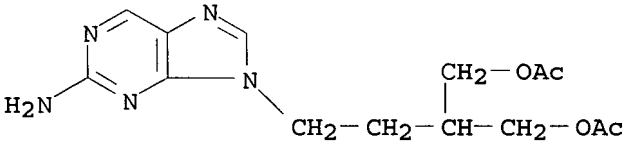
AB This invention relates to a topical pharmaceutical formulation suitable for use in treating virus infections of the skin and mucosa, and in particular it relates to topical formulations containing compds. having antiviral activity, particularly those active against Herpes Simplex Virus, with the exception of aciclovir. The formulations are oil-in-water topical pharmaceutical formulations comprising a dispersed oil phase and a continuous aqueous phase comprising water, solubilized antiviral compound and at least 10 % of diethylene glycol monoethyl ether. The antiviral compound is selected from penciclovir, famciclovir, ganciclovir, idoxuridine, foscarnet, ribavirin, and cidofovir. The formulations exhibit enhanced efficacy together with low irritancy and good phys. stability. A topical emulsion contained diethylene glycol monoethyl ether (Transcutol) 40, antiviral compound 5, stearyl alc. 5, cetyl alc. 4, light mineral oil 10.2, Brij 721 2.5, Brij 72 2.3, and purified water to 100 %.

IT 82410-32-0, Ganciclovir 104227-87-4, Famciclovir 113852-37-2, Cidofovir
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(topical emulsions containing antiviral compds. and diethylene glycol monoethyl ether)

RN 82410-32-0 HCAPLUS
CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]- (CA INDEX NAME)

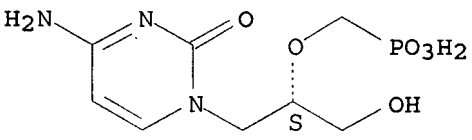


RN 104227-87-4 HCAPLUS
CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-, 1,3-diacetate (CA INDEX NAME)



RN 113852-37-2 HCAPLUS
CN Phosphonic acid, P-[[(1S)-2-(4-amino-2-oxo-1(2H)-pyrimidinyl)-1-(hydroxymethyl)ethoxy]methyl]- (CA INDEX NAME)

Absolute stereochemistry.



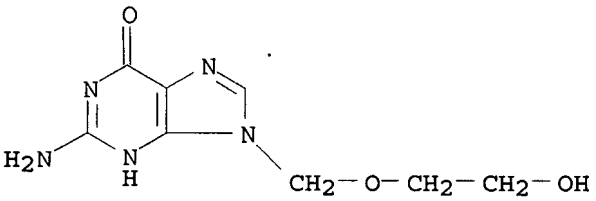
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 18 OF 23 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:121436 HCAPLUS <<LOGINID::20070502>>
DOCUMENT NUMBER: 128:239028
TITLE: Successful treatment of an acyclovir- and foscarnet-resistant herpes simplex virus type 1 lesion with intravenous cidofovir
AUTHOR(S): LoPresti, Antonia E.; Levine, Jerome F.; Munk, Gary B.; Tai, Chun Y.; Mendel, Dirk B.
CORPORATE SOURCE: Infectious dease Div., Dept. of Internal Medicine and Virology Laboratory, Hackensack University Medical Center, Hackensack, NJ, USA
SOURCE: Clinical Infectious Diseases (1998), 26(2), 512-513
CODEN: CIDIEL; ISSN: 1058-4838
PUBLISHER: University of Chicago Press
DOCUMENT TYPE: Journal
LANGUAGE: English

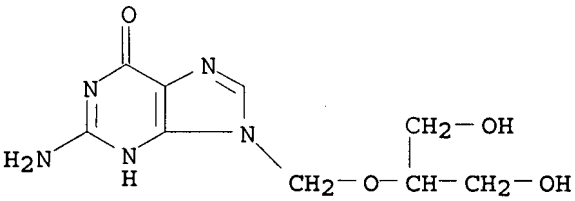
AB This report describes the successful use of i.v. cidofovir to effect rapid and complete resolution of an acyclovir- and foscarnet -resistant HSV-1 lesion in a patient who underwent umbilical cord stem-cell transplantation and who had severe unremitting mucositis of the oropharynx. Treatments with acyclovir, foscarnet and ganciclovir all failed to resolve the mucositis. I.v. cidofovir (5 mg/kg once weekly) with concomitant probenecid therapy was administered, in addition to hydration to reduce the risk of nephrotoxicity. Following three consecutive once-weekly doses of cidofovir, the mucositis cleared. Drug susceptibilities of four HSV isolates obtained from the patient after each antiviral agent revealed increased resistance to acyclovir, foscarnet and ganciclovir following administration of these antivirals. This case suggests potential value of the approved i.v. formulation of cidofovir for the treatment of HSV-1 lesions that are unresponsive to acyclovir and/or foscarnet therapy.

IT 59277-89-3, Acyclovir 82410-32-0, Ganciclovir
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cidofovir treatment of an acyclovir- and foscarnet -resistant herpes simplex virus type 1 lesion in a human)

RN 59277-89-3 HCAPLUS
CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]- (CA INDEX NAME)

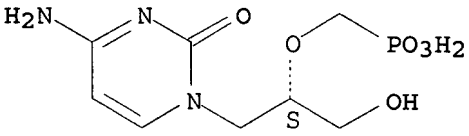


RN 82410-32-0 HCAPLUS
CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]- (CA INDEX NAME)



IT 113852-37-2, Cidofovir
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cidofovir treatment of an acyclovir- and foscarnet -resistant herpes simplex virus type 1 lesion in a human)
RN 113852-37-2 HCAPLUS
CN Phosphonic acid, P-[[(1S)-2-(4-amino-2-oxo-1(2H)-pyrimidinyl)-1-(hydroxymethyl)ethoxy]methyl]- (CA INDEX NAME)

Absolute stereochemistry.

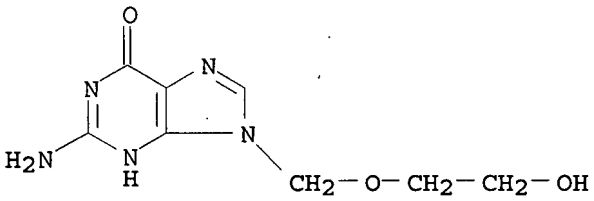


REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

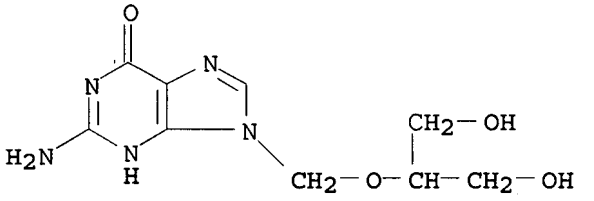
L28 ANSWER 19 OF 23 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:791030 HCAPLUS <<LOGINID::20070502>>
DOCUMENT NUMBER: 128:86368
TITLE: Antiviral drug susceptibility of human herpesvirus 8
AUTHOR(S): Neyts, Johan; De Clercq, Erik
CORPORATE SOURCE: Rega Institute for Medical Research, Katholieke Universiteit Leuven, Louvain, B-3000, Belg.
SOURCE: Antimicrobial Agents and Chemotherapy (1997), 41(12), 2754-2756
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors studied the susceptibility of human herpesvirus 8 (HHV-8) to a number of antiherpesvirus agents. The acyclic nucleoside phosphonate (ANP) analogs cidofovir and HPMPA [(S)-1-(3-hydroxy-2-phosphonylmethoxypropyl)adenine] effected potent inhibition of HHV-8 DNA synthesis, with 50% effective concns. (EC50) of 6.3 and 0.6 μM, resp. Adefovir, an ANP with both antiretrovirus and antiherpesvirus activity, blocked HHV-8 DNA replication at a fourfold-lower concentration than did foscarnet (EC50 of 39 and 177 μM, resp.). The most potent inhibitory effect was obtained with the N-7-substituted nucleoside analog S2242 (EC50, 0.11 μM). The nucleoside analogs acyclovir, penciclovir, H2G {(R)-9-[4-hydroxy-2-(hydroxymethyl) butyl]guanine}, and brivudine had weak to moderate effects (EC50 of ≥75, 43, 42, and 24 μM, resp., and EC90 of ≥75 μM), whereas ganciclovir elicited pronounced anti-HHV-8 activity (EC50, 8.9 μM).
IT 59277-89-3, Acyclovir 82410-32-0, Ganciclovir 106941-25-7, Adefovir 113852-37-2, Cidofovir
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiviral drug susceptibility of human herpesvirus 8)

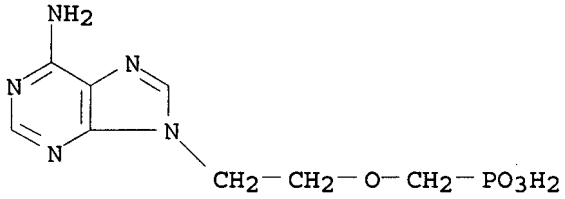
RN 59277-89-3 HCAPLUS
CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]- (CA INDEX NAME)



RN 82410-32-0 HCAPLUS
CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]- (CA INDEX NAME)

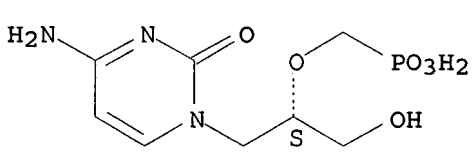


RN 106941-25-7 HCAPLUS
CN Phosphonic acid, P-[[2-(6-amino-9H-purin-9-yl)ethoxy]methyl]- (CA INDEX NAME)



RN 113852-37-2 HCAPLUS
CN Phosphonic acid, P-[[(1S)-2-(4-amino-2-oxo-1(2H)-pyrimidinyl)-1-(hydroxymethyl)ethoxy]methyl]- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS

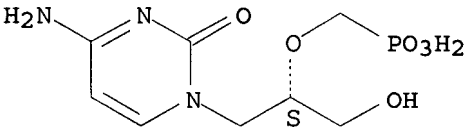
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 20 OF 23 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:634593 HCAPLUS <<LOGINID::20070502>>
DOCUMENT NUMBER: 127:287747
TITLE: Clinical uses of cidofovir
AUTHOR(S): Safrin, Sharon; Cherrington, Julie; Jaffe, Howard S.
CORPORATE SOURCE: Gilead Sciences, Foster City, CA, USA
SOURCE: Reviews in Medical Virology (1997), 7(3), 145-156
CODEN: RMVIEW; ISSN: 1052-9276
PUBLISHER: Wiley
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Cidofovir is a cytidine nucleotide analog recently licensed as an i.v. treatment for CMV retinitis in AIDS patients. Three controlled clin. trials have demonstrated efficacy of cidofovir for this indication, and have generated data useful as a guideline to prevent potential toxicity. Although de novo emergence of resistance to cidofovir has not been observed clin. in patients receiving cidofovir, cross-resistance to cidofovir in ganciclovir-resistant clin. DNA polymerase mutants has been identified. Cross-resistance of cidofovir and foscarnet has not been identified to date. A broad spectrum agent with in vitro activity against human herpesviruses, adenovirus, HPV, polyomaviruses and human poxviruses, cidofovir is under clin. investigation for a variety of potential applications. Examples include i.v. administration of cidofovir for treatment of progressive multifocal leukoencephalopathy and Kaposi's sarcoma, intraocular injection for treatment of CMV retinitis, intralesional injection for treatment of respiratory papillomatosis, topical application for treatment of molluscum contagiosum, anogenital condyloma acuminata, and recurrent genital herpes, and ophthalmic instillation for treatment of viral keratoconjunctivitis.

IT 113852-37-2, Cidofovir
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(clin. uses of cidofovir in humans)
RN 113852-37-2 HCAPLUS
CN Phosphonic acid, P-[[(1S)-2-(4-amino-2-oxo-1(2H)-pyrimidinyl)-1-(hydroxymethyl)ethoxy]methyl]- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 74 THERE ARE 74 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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FULL ESTIMATED COST	121.07	286.71

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AND TECHNOLOGY CORPORATION, AND FACHINFORMATIONSZENTRUM KARLSRUHE

FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Apr 27, 2007 (20070427/UP).

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     (FILE 'HOME' ENTERED AT 15:58:27 ON 02 MAY 2007)

     FILE 'HCAPLUS' ENTERED AT 15:58:36 ON 02 MAY 2007
                E US20040259832/PN 25
L1             1 S E3

     FILE 'STNGUIDE' ENTERED AT 15:59:26 ON 02 MAY 2007

     FILE 'HCAPLUS' ENTERED AT 16:02:09 ON 02 MAY 2007
L2         43567 S (9002-06-6 OR 4408-78-0 OR 4428-95-9 OR 59277-89-3 OR  66341-
L3        237600 S (9002-89-5 OR  9004-34-6 OR 9005-25-8 OR 9012-36-6 OR 24980-4
L4        276194 S L2 OR L3
L5             1 S L4 AND L1

     FILE 'STNGUIDE' ENTERED AT 16:03:41 ON 02 MAY 2007

     FILE 'HCAPLUS' ENTERED AT 16:07:58 ON 02 MAY 2007
L6          6746 S  (59277-89-3 OR 66341-16-0 OR 82410-32-0 OR 86761-39-9 OR 104
                E HERPES+ALL/CT
L7          2471 S L6 AND (HERPES OR "HERPES" OR "INFECTION" (L) "HERPES" OR "SK
L8           113 S ACYCLOVIR ?PHOSPHATE?
L9            40 S L8 AND L7
L10           38 S L9 AND 1800<=PY<=2003
L11         9845 S THYMIDINE KINASE
L12           24 S L11 AND L10
L13           76 S THYMIDINE KINASE INHIBITOR
L14            0 S L13 AND L12
L15          684 S CIDOFOVIR
L16           89 S L15 AND L7
L17            0 S L16 AND L10
L18            0 S GANCILOVIR MONOPHOSPHATE
L19         3504 S GANCICLOVIR
L20           11 S GANCICLOVIR MONOPHOSPHATE
L21            2 S L20 AND L7

     FILE 'STNGUIDE' ENTERED AT 16:16:23 ON 02 MAY 2007

     FILE 'HCAPLUS' ENTERED AT 16:18:06 ON 02 MAY 2007
L22            3 S FORSCARNET
L23          857 S FOSCARNET
L24          121 S L23 AND L7
L25           93 S L24 AND 1800<=PY<=2003

     FILE 'STNGUIDE' ENTERED AT 16:19:38 ON 02 MAY 2007

     FILE 'HCAPLUS' ENTERED AT 16:20:46 ON 02 MAY 2007
L26           93 S L25 AND (L20 OR L16 OR L13 OR L24 OR L10)
L27            0 S L25 AND L20
L28           23 S L25 AND L16
L29            0 S L25 AND L13
```

10767019>05/05/2007

L30 93 S L25 AND L24
L31 1 S L25 AND L10

FILE 'STNGUIDE' ENTERED AT 16:23:15 ON 02 MAY 2007

=>
Connecting via Winsock to STN

Welcome to STN International! Enter x:x

LOGINID:ssptarpi1623

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS 1 Web Page URLs for STN Seminar Schedule - N. America
NEWS 2 JAN 08 CHEMLIST enhanced with New Zealand Inventory of Chemicals
NEWS 3 JAN 16 CA/CAplus Company Name Thesaurus enhanced and reloaded
NEWS 4 JAN 16 IPC version 2007.01 thesaurus available on STN
NEWS 5 JAN 16 WPIDS/WPINDEX/WPIX enhanced with IPC 8 reclassification data
NEWS 6 JAN 22 CA/CAplus updated with revised CAS roles
NEWS 7 JAN 22 CA/CAplus enhanced with patent applications from India
NEWS 8 JAN 29 PHAR reloaded with new search and display fields
NEWS 9 JAN 29 CAS Registry Number crossover limit increased to 300,000 in multiple databases
NEWS 10 FEB 15 PATDPASPC enhanced with Drug Approval numbers
NEWS 11 FEB 15 RUSSIAPAT enhanced with pre-1994 records
NEWS 12 FEB 23 KOREAPAT enhanced with IPC 8 features and functionality
NEWS 13 FEB 26 MEDLINE reloaded with enhancements
NEWS 14 FEB 26 EMBASE enhanced with Clinical Trial Number field
NEWS 15 FEB 26 TOXCENTER enhanced with reloaded MEDLINE
NEWS 16 FEB 26 IFICDB/IFIPAT/IFIUDB reloaded with enhancements
NEWS 17 FEB 26 CAS Registry Number crossover limit increased from 10,000 to 300,000 in multiple databases
NEWS 18 MAR 15 WPIDS/WPIX enhanced with new FRAGHITSTR display format
NEWS 19 MAR 16 CASREACT coverage extended
NEWS 20 MAR 20 MARPAT now updated daily
NEWS 21 MAR 22 LWPI reloaded
NEWS 22 MAR 30 RDISCLOSURE reloaded with enhancements
NEWS 23 APR 02 JICST-EPLUS removed from database clusters and STN
NEWS 24 APR 30 GENBANK reloaded and enhanced with Genome Project ID field
NEWS 25 APR 30 CHEMCATS enhanced with 1.2 million new records
NEWS 26 APR 30 CA/CAplus enhanced with 1870-1889 U.S. patent records
NEWS 27 APR 30 INPADOC replaced by INPADOCDB on STN
NEWS 28 MAY 01 New CAS web site launched

NEWS EXPRESS NOVEMBER 10 CURRENT WINDOWS VERSION IS V8.01c, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 25 SEPTEMBER 2006.

NEWS HOURS STN Operating Hours Plus Help Desk Availability
NEWS LOGIN Welcome Banner and News Items
NEWS IPC8 For general information regarding STN implementation of IPC 8

Enter NEWS followed by the item number or name to see news on that specific topic.

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* * * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 11:34:29 ON 03 MAY 2007

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LOGINID:ssptarpi1623

PASSWORD:
 * * * * * * RECONNECTED TO STN INTERNATIONAL * * * * * *
SESSION RESUMED IN FILE 'HOME' AT 11:36:51 ON 03 MAY 2007
FILE 'HOME' ENTERED AT 11:36:51 ON 03 MAY 2007
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       0.21       0.21

=> fil hcaplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       0.21       0.21

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=> fil reg
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       2.60       2.81

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```

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http://www.cas.org/support/stngen/stndoc/properties.html

=> S 161363-19-5/RN
L1 1 161363-19-5/RN

=> FIL CHEMCATS

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.45	3.26

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For details on recent updates in CHEMCATS, enter NEWS FILE at an arrow prompt. For the list of suppliers currently in the file, enter HELP SPA, HELP SPBC, HELP SPDH, HELP SPIN, HELP SPOP, and HELP SPQZ. For the list of current catalogs, enter HELP CTA, HELP CTBC, HELP CTDH, HELP CTIN, HELP CTOP, and HELP CTQZ.

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=> S L1
L2 0 L1

=> FIL REGISTRY

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.93	4.19

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on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html

=> fil hcaplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.45	4.64

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=> s l1
L3 11 L1

=> fil stng

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	2.60	7.24

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=> fil hcaplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.06	7.30

FILE 'HCAPLUS' ENTERED AT 11:39:06 ON 03 MAY 2007
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=> E "161363-19-5"/BI,RN 25

E1	2	161363-18-4/BI
E2	2	161363-18-4P/BI
E3	11 -->	161363-19-5/BI
E4	0	161363-19-5/RN
E5	1	161363-19-5D/BI
E6	3	161363-19-5P/BI
E7	3	161363-20-8/BI
E8	3	161363-20-8P/BI
E9	3	161363-21-9/BI
E10	1	161363-21-9P/BI
E11	1	161363-22-0/BI
E12	1	161363-22-0P/BI
E13	3	161363-23-1/BI
E14	3	161363-23-1P/BI
E15	3	161363-24-2/BI
E16	2	161363-24-2P/BI
E17	3	161363-25-3/BI
E18	1	161363-25-3P/BI
E19	3	161363-26-4/BI
E20	3	161363-26-4P/BI
E21	3	161363-27-5/BI
E22	3	161363-27-5P/BI
E23	1	161363-28-6/BI
E24	1	161363-28-6P/BI
E25	1	161363-29-7/BI

=> S E3 OR E5 OR E6
11 161363-19-5/BI

```
             1 161363-19-5D/BI
             3 161363-19-5P/BI
L4          11 161363-19-5/BI OR 161363-19-5D/BI OR 161363-19-5P/BI

=> s l4 not l3
L5           0 L4 NOT L3

=> d l4 ibib abs hitstr

L4   ANSWER 1 OF 11  HCAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:        2005:398777  HCAPLUS <<LOGINID::20070503>>
DOCUMENT NUMBER:         143:97319
TITLE:                   Inhibition of Herpes Simplex Virus Thymidine Kinases
                         by 2-Phenylamino-6-oxopurines and Related Compounds:
                         Structure-Activity Relationships and Antiherpetic
                         Activity in Vivo
AUTHOR(S):               Manikowski, Andrzej; Verri, Annalisa; Lossani, Andrea;
                         Gebhardt, Bryan M.; Gambino, Joseph; Focher, Federico;
                         Spadari, Silvio; Wright, George E.
CORPORATE SOURCE:        GLSynthesis Inc., Worcester, MA, 01605, USA
SOURCE:                  Journal of Medicinal Chemistry (2005), 48(11),
                         3919-3929
                         CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER:               American Chemical Society
DOCUMENT TYPE:           Journal
LANGUAGE:                English
OTHER SOURCE(S):         CASREACT 143:97319
GI
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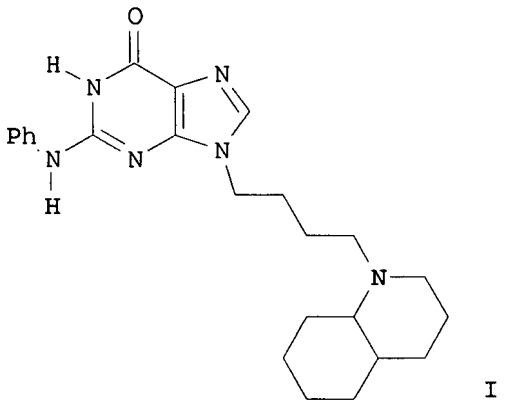


I

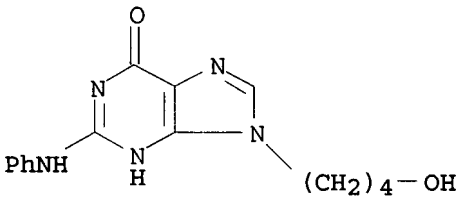
AB Derivs. of the herpes simplex thymidine kinase inhibitor HBPG [2-phenylamino-9-(4-hydroxybutyl)-6-oxopurine] have been synthesized and tested for inhibitory activity against recombinant enzymes (TK) from herpes simplex types 1 and 2 (HSV-1, HSV-2). The compds. inhibited phosphorylation of [3H]thymidine by both enzymes, but potencies differed quant. from those of HBPG and were generally greater for HSV-2 than HSV-1 TKs. Changes in inhibitory potency were generally consistent with the inhibitor/substrate binding site structure based on published X-ray structures of HSV-1 TK. In particular, several 9-(4-aminobutyl) analogs with bulky tertiary amino substituents were among the most potent inhibitors. Variable substrate assays showed that the most potent compound, 2-phenylamino-9-[4-(1-decahydroquinolyl)butyl]-6-oxopurine (I·2 HCl), was a competitive inhibitor, with Ki values of 0.03 and 0.005 μM

against HSV-1 and HSV-2 TKs, resp. The parent compound HBPG was uniquely active in viral infection models in mice, both against ocular HSV-2 reactivation and against HSV-1 and HSV-2 encephalitis. In assays lacking [3H]thymidine, HBPG was found to be an efficient substrate for the enzymes. The ability of the TKs to phosphorylate HBPG may relate to its antiherpetic activity in vivo.

IT 161363-19-5
RL: PAC (Pharmacological activity); RCT (Reactant); BIOL (Biological study); RACT (Reactant or reagent)
(inhibition of herpes simplex virus thymidine kinases by 2-phenylamino-6-oxopurines and related compds., structure-activity relationships and antiherpetic activity in vivo)

RN 161363-19-5 HCAPLUS

CN 6H-Purin-6-one, 1,9-dihydro-9-(4-hydroxybutyl)-2-(phenylamino)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> fil stng

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=> fil hcaplus

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FULL ESTIMATED COST	0.24	18.01

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
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=> E "4408-78-0"/BI,RN 25
E1            1     4408-75-7/BI
E2            2     4408-77-9/BI
E3          648 --> 4408-78-0/BI
E4            0     4408-78-0/RN
E5           47     4408-78-0D/BI
E6           14     4408-78-0DP/BI
E7           45     4408-78-0P/BI
E8          398     4408-81-5/BI
E9          135     4408-81-5D/BI
E10          28     4408-81-5DP/BI
E11          36     4408-81-5P/BI
E12           9     4408-82-6/BI
E13           6     4408-82-6P/BI
E14           3     4408-85-9/BI
E15           1     4408-85-9D/BI
E16           1     4408-86-0/BI
E17           1     4408-92-8/BI
E18           1     4408-92-8P/BI
E19           2     4408-93-9/BI
E20           1     4408-95-1/BI
E21           1     4408-95-1P/BI
E22          71     4408-96-2/BI
E23          69     4408-96-2P/BI
E24           5     4408-97-3/BI
E25           5     4408-97-3P/BI

=> S E3 OR E5 OR E6 OR E7
            648 4408-78-0/BI
             47 4408-78-0D/BI
             14 4408-78-0DP/BI
             45 4408-78-0P/BI
L6          648 4408-78-0/BI OR 4408-78-0D/BI OR 4408-78-0DP/BI OR 4408-78-0P/BI

=> E "4428-95-9"/BI,RN 25
E1           11     4428-38-0P/BI
E2            2     4428-39-1/BI
E3         1041 --> 4428-95-9/BI
E4            0     4428-95-9/RN
E5           54     4428-95-9D/BI
E6           11     4428-95-9DP/BI
E7           25     4428-95-9P/BI
E8           63     4428-98-2/BI
E9            8     4428-98-2P/BI
E10           1     44280/BI
E11           2     44280-42-4/BI
```

```
E12           2     44280-42-4P/BI
E13           2     44281/BI
E14           1     442816/BI
E15           1     4428178/BI
E16           1     4428229/BI
E17           1     4428246/BI
E18           1     44283/BI
E19           1     442830-09-3/BI
E20           1     4428301/BI
E21           1     4428383/BI
E22           2     44283G/BI
E23           1     44284/BI
E24           1     442842-28-6/BI
E25           1     442842-29-7/BI

=> S E3 OR E5 OR E6 OR E7
          1041 4428-95-9/BI
            54 4428-95-9D/BI
            11 4428-95-9DP/BI
            25 4428-95-9P/BI
L7        1041 4428-95-9/BI OR 4428-95-9D/BI OR 4428-95-9DP/BI OR 4428-95-9P/BI

=> E "59277-89-3"/BI,RN 25
E1            3     59277-88-2/BI
E2            3     59277-88-2P/BI
E3         3560 --> 59277-89-3/BI
E4            0     59277-89-3/RN
E5          161     59277-89-3D/BI
E6           74     59277-89-3DP/BI
E7          163     59277-89-3P/BI
E8            4     59277-90-6/BI
E9            3     59277-90-6P/BI
E10           8     59277-91-7/BI
E11           5     59277-91-7P/BI
E12           6     59277-92-8/BI
E13           6     59277-92-8P/BI
E14           4     59277-93-9/BI
E15           4     59277-93-9P/BI
E16           2     59277-94-0/BI
E17           1     59277-94-0P/BI
E18           3     59277-95-1/BI
E19           3     59277-95-1P/BI
E20           5     59277-96-2/BI
E21           3     59277-96-2P/BI
E22           3     59277-97-3/BI
E23           3     59277-97-3P/BI
E24           5     59277-98-4/BI
E25           5     59277-98-4P/BI

=> S E3 OR E5 OR E6 OR E7
          3560 59277-89-3/BI
           161 59277-89-3D/BI
            74 59277-89-3DP/BI
           163 59277-89-3P/BI
L8        3560 59277-89-3/BI OR 59277-89-3D/BI OR 59277-89-3DP/BI OR 59277-89-3P/BI

=> E "66341-16-0"/BI,RN 25
E1            5     66341-15-9/BI
E2            3     66341-15-9P/BI
E3           68 --> 66341-16-0/BI
E4            0     66341-16-0/RN
E5           12     66341-16-0D/BI
E6            8     66341-16-0DP/BI
```

```
E7           26     66341-16-0P/BI
E8           30     66341-17-1/BI
E9            2     66341-17-1D/BI
E10           1     66341-17-1DP/BI
E11           3     66341-17-1P/BI
E12         102     66341-18-2/BI
E13           2     66341-18-2D/BI
E14           7     66341-18-2P/BI
E15           1     66341-19-3/BI
E16           1     66341-19-3P/BI
E17           3     66341-20-6/BI
E18           3     66341-20-6P/BI
E19           1     66341-21-7/BI
E20           1     66341-21-7P/BI
E21           1     66341-22-8/BI
E22           1     66341-22-8P/BI
E23           1     66341-24-0/BI
E24           1     66341-24-0P/BI
E25           1     66341-25-1/BI

=> S E3 OR E5 OR E6 OR E7
             68 66341-16-0/BI
             12 66341-16-0D/BI
              8 66341-16-0DP/BI
             26 66341-16-0P/BI
L9           68 66341-16-0/BI OR 66341-16-0D/BI OR 66341-16-0DP/BI OR 66341-16-0P/BI

=> E "82410-32-0"/BI,RN 25
E1           18     82410-31-9/BI
E2           13     82410-31-9P/BI
E3         3177 --> 82410-32-0/BI
E4            0     82410-32-0/RN
E5           81     82410-32-0D/BI
E6           29     82410-32-0DP/BI
E7           80     82410-32-0P/BI
E8            6     82410-33-1/BI
E9            2     82410-33-1P/BI
E10           1     82410-34-2/BI
E11           1     82410-34-2P/BI
E12           7     82410-35-3/BI
E13           2     82410-35-3P/BI
E14           1     82410-36-4/BI
E15           1     82410-36-4P/BI
E16           1     82410-37-5/BI
E17           1     82410-37-5P/BI
E18           1     82410-38-6/BI
E19           1     82410-38-6P/BI
E20           1     82410-39-7/BI
E21           1     82410-39-7P/BI
E22           1     82410-40-0/BI
E23           1     82410-40-0P/BI
E24           1     82410-41-1/BI
E25           1     82410-41-1P/BI

=> S E3 OR E5 OR E6 OR E7
           3177 82410-32-0/BI
             81 82410-32-0D/BI
             29 82410-32-0DP/BI
             80 82410-32-0P/BI
L10        3177 82410-32-0/BI OR 82410-32-0D/BI OR 82410-32-0DP/BI OR 82410-32-0P/BI

=> E "86761-39-9"/BI,RN 25
E1           36     86761-38-8/BI
```

```
E2            3      86761-38-8P/BI
E3           22  --> 86761-39-9/BI
E4            0      86761-39-9/RN
E5            1      86761-39-9D/BI
E6            5      86761-39-9P/BI
E7            1      86761-40-2/BI
E8            1      86761-41-3/BI
E9            1      86761-41-3P/BI
E10           1      86761-42-4/BI
E11           1      86761-42-4P/BI
E12           4      86761-43-5/BI
E13           1      86761-44-6/BI
E14           1      86761-45-7/BI
E15           1      86761-45-7P/BI
E16           1      86761-46-8/BI
E17           1      86761-46-8P/BI
E18           1      86761-47-9/BI
E19           1      86761-47-9P/BI
E20           1      86761-48-0/BI
E21           1      86761-48-0P/BI
E22           1      86761-49-1/BI
E23           1      86761-49-1P/BI
E24           1      86761-50-4/BI
E25           1      86761-50-4P/BI

=> S E3 OR E5 OR E6
            22 86761-39-9/BI
             1 86761-39-9D/BI
             5 86761-39-9P/BI
L11         22 86761-39-9/BI OR 86761-39-9D/BI OR 86761-39-9P/BI

=> E "104227-87-4"/BI,RN 25
E1          34      104227-86-3/BI
E2          17      104227-86-3P/BI
E3         544  --> 104227-87-4/BI
E4           0      104227-87-4/RN
E5          17      104227-87-4D/BI
E6           3      104227-87-4DP/BI
E7          45      104227-87-4P/BI
E8          12      104227-88-5/BI
E9           6      104227-88-5P/BI
E10          8      104227-89-6/BI
E11          8      104227-89-6P/BI
E12          5      104227-90-9/BI
E13          5      104227-90-9P/BI
E14          1      104227-91-0/BI
E15          1      104227-91-0P/BI
E16          1      104227-92-1/BI
E17          1      104227-92-1P/BI
E18          4      104227-93-2/BI
E19          4      104227-93-2P/BI
E20          4      104227-94-3/BI
E21          4      104227-94-3P/BI
E22          4      104227-95-4/BI
E23          4      104227-95-4P/BI
E24          3      104227-96-5/BI
E25          3      104227-96-5P/BI

=> S E3 OR E5 OR E6 OR E7
           544 104227-87-4/BI
            17 104227-87-4D/BI
             3 104227-87-4DP/BI
            45 104227-87-4P/BI
```

```
L12         544 104227-87-4/BI OR 104227-87-4D/BI OR 104227-87-4DP/BI OR 104227-87-4P/BI

=> E "161363-19-5"/BI,RN 25
E1            2     161363-18-4/BI
E2            2     161363-18-4P/BI
E3           11 --> 161363-19-5/BI
E4            0     161363-19-5/RN
E5            1     161363-19-5D/BI
E6            3     161363-19-5P/BI
E7            3     161363-20-8/BI
E8            3     161363-20-8P/BI
E9            3     161363-21-9/BI
E10           1     161363-21-9P/BI
E11           1     161363-22-0/BI
E12           1     161363-22-0P/BI
E13           3     161363-23-1/BI
E14           3     161363-23-1P/BI
E15           3     161363-24-2/BI
E16           2     161363-24-2P/BI
E17           3     161363-25-3/BI
E18           1     161363-25-3P/BI
E19           3     161363-26-4/BI
E20           3     161363-26-4P/BI
E21           3     161363-27-5/BI
E22           3     161363-27-5P/BI
E23           1     161363-28-6/BI
E24           1     161363-28-6P/BI
E25           1     161363-29-7/BI

=> S E3 OR E5 OR E6
             11 161363-19-5/BI
              1 161363-19-5D/BI
              3 161363-19-5P/BI
L13          11 161363-19-5/BI OR 161363-19-5D/BI OR 161363-19-5P/BI

=> E "113852-37-2"/BI,RN 25
E1            9     113852-36-1/BI
E2            4     113852-36-1P/BI
E3          687 --> 113852-37-2/BI
E4            0     113852-37-2/RN
E5           28     113852-37-2D/BI
E6            8     113852-37-2DP/BI
E7           27     113852-37-2P/BI
E8            8     113852-38-3/BI
E9            2     113852-38-3P/BI
E10           3     113852-39-4/BI
E11           1     113852-39-4P/BI
E12           4     113852-40-7/BI
E13           3     113852-40-7P/BI
E14         100     113852-41-8/BI
E15           1     113852-41-8D/BI
E16           9     113852-41-8P/BI
E17          16     113852-42-9/BI
E18           7     113852-42-9P/BI
E19           7     113852-43-0/BI
E20           2     113852-43-0P/BI
E21           3     113852-44-1/BI
E22           1     113852-44-1P/BI
E23           5     113852-46-3/BI
E24           1     113852-46-3P/BI
E25           2     113852-47-4/BI

=> S E3 OR E5 OR E6 OR E7
```

```
            687 113852-37-2/BI
             28 113852-37-2D/BI
              8 113852-37-2DP/BI
             27 113852-37-2P/BI
L14         687 113852-37-2/BI OR 113852-37-2D/BI OR 113852-37-2DP/BI OR 113852-37-2P/BI

=> E "106941-25-7"/BI,RN 25
E1            2     106941-23-5P/BI
E2            1     106941-24-6/BI
E3          648 --> 106941-25-7/BI
E4            0     106941-25-7/RN
E5           27     106941-25-7D/BI
E6            8     106941-25-7DP/BI
E7           42     106941-25-7P/BI
E8            1     106941-26-8/BI
E9            3     106941-27-9/BI
E10           1     106941-28-0/BI
E11           1     106941-28-0P/BI
E12           1     106941-29-1/BI
E13           1     106941-29-1P/BI
E14           1     106941-30-4/BI
E15           1     106941-30-4P/BI
E16           1     106941-31-5/BI
E17           1     106941-31-5P/BI
E18           1     106941-32-6/BI
E19           1     106941-32-6P/BI
E20           4     106941-33-7/BI
E21           3     106941-33-7P/BI
E22           1     106941-34-8/BI
E23           2     106941-35-9/BI
E24           1     106941-35-9P/BI
E25           2     106941-36-0/BI

=> S E3 OR E5 OR E6 OR E7
            648 106941-25-7/BI
             27 106941-25-7D/BI
              8 106941-25-7DP/BI
             42 106941-25-7P/BI
L15         648 106941-25-7/BI OR 106941-25-7D/BI OR 106941-25-7DP/BI OR 106941-25-7P/BI

=> d his

     (FILE 'HOME' ENTERED AT 11:34:29 ON 03 MAY 2007)

     FILE 'HCAPLUS' ENTERED AT 11:37:07 ON 03 MAY 2007

     FILE 'REGISTRY' ENTERED AT 11:37:33 ON 03 MAY 2007
L1             1 S 161363-19-5/RN

     FILE 'CHEMCATS' ENTERED AT 11:37:59 ON 03 MAY 2007
                SET LIN 80
L2             0 S L1

     FILE 'REGISTRY' ENTERED AT 11:38:09 ON 03 MAY 2007

     FILE 'HCAPLUS' ENTERED AT 11:38:36 ON 03 MAY 2007
L3            11 S L1

     FILE 'STNGUIDE' ENTERED AT 11:38:44 ON 03 MAY 2007

     FILE 'HCAPLUS' ENTERED AT 11:39:06 ON 03 MAY 2007
                E "161363-19-5"/BI,RN 25
L4            11 S E3 OR E5 OR E6
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L5            0 S L4 NOT L3

     FILE 'STNGUIDE' ENTERED AT 11:40:03 ON 03 MAY 2007

     FILE 'HCAPLUS' ENTERED AT 11:42:16 ON 03 MAY 2007
                E "4408-78-0"/BI,RN 25
L6           648 S E3 OR E5 OR E6 OR E7
                E "4428-95-9"/BI,RN 25
L7          1041 S E3 OR E5 OR E6 OR E7
                E "59277-89-3"/BI,RN 25
L8          3560 S E3 OR E5 OR E6 OR E7
                E "66341-16-0"/BI,RN 25
L9            68 S E3 OR E5 OR E6 OR E7
                E "82410-32-0"/BI,RN 25
L10         3177 S E3 OR E5 OR E6 OR E7
                E "86761-39-9"/BI,RN 25
L11           22 S E3 OR E5 OR E6
                E "104227-87-4"/BI,RN 25
L12          544 S E3 OR E5 OR E6 OR E7
                E "161363-19-5"/BI,RN 25
L13           11 S E3 OR E5 OR E6
                E "113852-37-2"/BI,RN 25
L14          687 S E3 OR E5 OR E6 OR E7
                E "106941-25-7"/BI,RN 25
L15          648 S E3 OR E5 OR E6 OR E7

=> s l4 and l6
L16           1 L4 AND L6

=> d l16 ibib abs hitstr

L16  ANSWER 1 OF 1  HCAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:         2004:681513  HCAPLUS <<LOGINID::20070503>>
DOCUMENT NUMBER:          141:185078
TITLE:                    Novel antiherpes drug combinations of Herpes simplex
                          virus thymidine kinase inhibitors and antiherpes
                          substances
INVENTOR(S):              Wright, George E.
PATENT ASSIGNEE(S):       University of Massachusetts, USA
SOURCE:                   PCT Int. Appl., 22 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
     ---------------      ----   --------    --------------------    --------
     WO 2004069168         A2    20040819    WO 2004-US2427          20040129
     WO 2004069168         A3    20050915
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI
         RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE,
             BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU,
             MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN,
             GQ, GW, ML, MR, NE, SN, TD, TG
     CA 2514334            A1    20040819    CA 2004-2514334         20040129
     US 2004259832         A1    20041223    US 2004-767019          20040129
     EP 1594507            A2    20051116    EP 2004-706459          20040129
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
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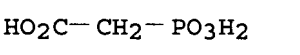
PRIORITY APPLN. INFO.: US 2003-443519P P 20030129
WO 2004-US2427 W 20040129

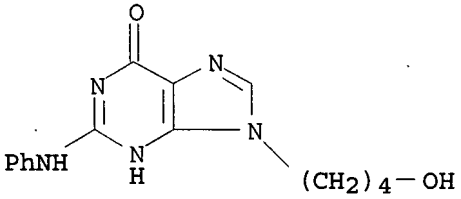
AB Composition and methods are disclosed that include a synergistic combination of an inhibitor of Herpes simplex virus thymidine kinase, and an antiherpes substance. The effect of combination of 2-phenylamino-9-(4-hydroxybutyl)-6-oxopurine and foscarnet against HSV2 encephalitis in mice was examined

IT 4408-78-0 161363-19-5
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiherpes drug combinations of Herpes simplex virus thymidine kinase inhibitors and antiherpes substances)

RN 4408-78-0 HCAPLUS
CN Acetic acid, 2-phosphono- (CA INDEX NAME)



RN 161363-19-5 HCAPLUS
CN 6H-Purin-6-one, 1,9-dihydro-9-(4-hydroxybutyl)-2-(phenylamino)- (9CI) (CA INDEX NAME)



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(FILE 'HOME' ENTERED AT 11:34:29 ON 03 MAY 2007)

FILE 'HCAPLUS' ENTERED AT 11:37:07 ON 03 MAY 2007

FILE 'REGISTRY' ENTERED AT 11:37:33 ON 03 MAY 2007
L1 1 S 161363-19-5/RN

FILE 'CHEMCATS' ENTERED AT 11:37:59 ON 03 MAY 2007
SET LIN 80
L2 0 S L1

FILE 'REGISTRY' ENTERED AT 11:38:09 ON 03 MAY 2007

FILE 'HCAPLUS' ENTERED AT 11:38:36 ON 03 MAY 2007
L3 11 S L1

FILE 'STNGUIDE' ENTERED AT 11:38:44 ON 03 MAY 2007

FILE 'HCAPLUS' ENTERED AT 11:39:06 ON 03 MAY 2007
E "161363-19-5"/BI,RN 25
L4 11 S E3 OR E5 OR E6
L5 0 S L4 NOT L3

FILE 'STNGUIDE' ENTERED AT 11:40:03 ON 03 MAY 2007

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     FILE 'HCAPLUS' ENTERED AT 11:42:16 ON 03 MAY 2007
                E "4408-78-0"/BI,RN 25
L6           648 S E3 OR E5 OR E6 OR E7
                E "4428-95-9"/BI,RN 25
L7          1041 S E3 OR E5 OR E6 OR E7
                E "59277-89-3"/BI,RN 25
L8          3560 S E3 OR E5 OR E6 OR E7
                E "66341-16-0"/BI,RN 25
L9            68 S E3 OR E5 OR E6 OR E7
                E "82410-32-0"/BI,RN 25
L10         3177 S E3 OR E5 OR E6 OR E7
                E "86761-39-9"/BI,RN 25
L11           22 S E3 OR E5 OR E6
                E "104227-87-4"/BI,RN 25
L12          544 S E3 OR E5 OR E6 OR E7
                E "161363-19-5"/BI,RN 25
L13           11 S E3 OR E5 OR E6
                E "113852-37-2"/BI,RN 25
L14          687 S E3 OR E5 OR E6 OR E7
                E "106941-25-7"/BI,RN 25
L15          648 S E3 OR E5 OR E6 OR E7
L16            1 S L4 AND L6

=> s l4 and l7
L17            1 L4 AND L7

=> s l4 and l8
L18            5 L4 AND L8

=> s l17 not l16
L19            0 L17 NOT L16

=> s l18 not l16
L20            4 L18 NOT L16

=> d l20 ibib abs hitstr 1-4

L20  ANSWER 1 OF 4  HCAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:         2005:398777  HCAPLUS <<LOGINID::20070503>>
DOCUMENT NUMBER:          143:97319
TITLE:                    Inhibition of Herpes Simplex Virus Thymidine Kinases
                          by 2-Phenylamino-6-oxopurines and Related Compounds:
                          Structure-Activity Relationships and Antiherpetic
                          Activity in Vivo
AUTHOR(S):                Manikowski, Andrzej; Verri, Annalisa; Lossani, Andrea;
                          Gebhardt, Bryan M.; Gambino, Joseph; Focher, Federico;
                          Spadari, Silvio; Wright, George E.
CORPORATE SOURCE:         GLSynthesis Inc., Worcester, MA, 01605, USA
SOURCE:                   Journal of Medicinal Chemistry (2005), 48(11),
                          3919-3929
                          CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER:                American Chemical Society
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
OTHER SOURCE(S):          CASREACT 143:97319
GI
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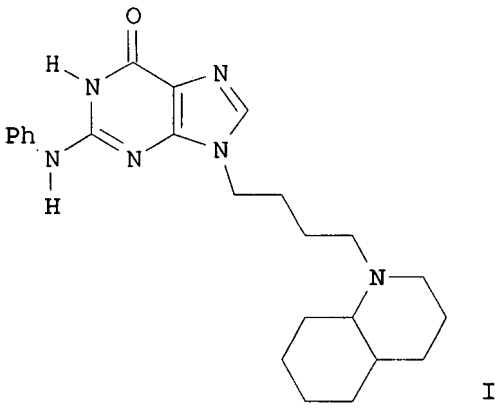


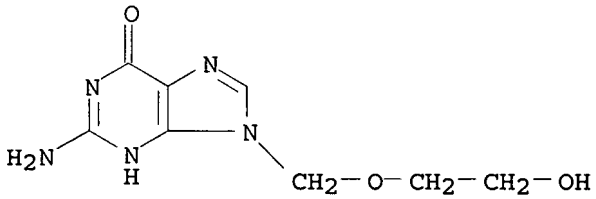
I

AB Derivs. of the herpes simplex thymidine kinase inhibitor HBPG [2-phenylamino-9-(4-hydroxybutyl)-6-oxopurine] have been synthesized and tested for inhibitory activity against recombinant enzymes (TK) from herpes simplex types 1 and 2 (HSV-1, HSV-2). The compds. inhibited phosphorylation of [3H]thymidine by both enzymes, but potencies differed quant. from those of HBPG and were generally greater for HSV-2 than HSV-1 TKs. Changes in inhibitory potency were generally consistent with the inhibitor/substrate binding site structure based on published X-ray structures of HSV-1 TK. In particular, several 9-(4-aminobutyl) analogs with bulky tertiary amino substituents were among the most potent inhibitors. Variable substrate assays showed that the most potent compound, 2-phenylamino-9-[4-(1-decahydroquinolyl)butyl]-6-oxopurine (I·2 HCl), was a competitive inhibitor, with Ki values of 0.03 and 0.005 μM against HSV-1 and HSV-2 TKs, resp. The parent compound HBPG was uniquely active in viral infection models in mice, both against ocular HSV-2 reactivation and against HSV-1 and HSV-2 encephalitis. In assays lacking [3H]thymidine, HBPG was found to be an efficient substrate for the enzymes. The ability of the TKs to phosphorylate HBPG may relate to its antiherpetic activity in vivo.

IT 59277-89-3, Acyclovir
RL: PAC (Pharmacological activity); BIOL (Biological study)
(inhibition of herpes simplex virus thymidine kinases by 2-phenylamino-6-oxopurines and related compds., structure-activity relationships and antiherpetic activity in vivo)

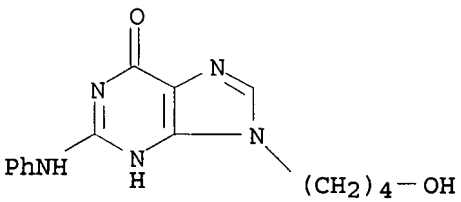
RN 59277-89-3 HCAPLUS

CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]- (CA INDEX NAME)



IT 161363-19-5
RL: PAC (Pharmacological activity); RCT (Reactant); BIOL (Biological study); RACT (Reactant or reagent)
(inhibition of herpes simplex virus thymidine kinases by 2-phenylamino-6-oxopurines and related compds., structure-activity relationships and antiherpetic activity in vivo)

RN 161363-19-5 HCAPLUS
CN 6H-Purin-6-one, 1,9-dihydro-9-(4-hydroxybutyl)-2-(phenylamino)- (9CI) (CA INDEX NAME)



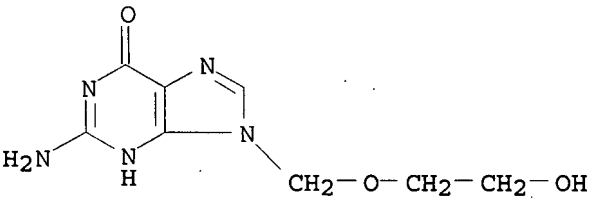
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:134376 HCAPLUS <<LOGINID::20070503>>
DOCUMENT NUMBER: 142:366752
TITLE: Binding Mode Prediction of Cytochrome P450 and Thymidine Kinase Protein-Ligand Complexes by Consideration of Water and Rescoring in Automated Docking
AUTHOR(S): de Graaf, Chris; Pospisil, Pavel; Pos, Wouter; Folkers, Gerd; Vermeulen, Nico P. E.
CORPORATE SOURCE: Leiden/Amsterdam Center for Drug Research, Division of Molecular Toxicology, Vrije Universiteit Amsterdam, Amsterdam, 1081 HV, Neth.
SOURCE: Journal of Medicinal Chemistry (2005), 48(7), 2308-2318
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

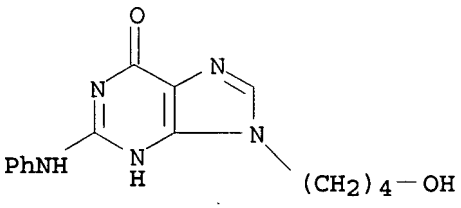
AB The popular docking programs AutoDock, FlexX, and GOLD were used to predict binding modes of ligands in crystallog. complexes including x-ray water mols. or computationally predicted water mols. Isoenzymes of two different enzyme systems were used, namely cytochromes P 450 (n = 19) and thymidine kinases (n = 19) and three different "water" scenarios: i.e., docking (i) into water-free active sites, (ii) into active sites containing crystallog. water mols., and (iii) into active sites containing water mols. predicted by a novel approach based on the program GRID. Docking accuracies were determined in terms of the root-mean-square deviation (RMSD) accuracy and, newly defined, in terms of the ligand catalytic site prediction (CSP) accuracy. Consideration of both x-ray and predicted water mols. and the subsequent pooling and rescoring of all solns. (generated by all three docking programs) with the SCORE scoring function significantly improved the quality of prediction of the binding modes both in terms of RMSD and CSP accuracy.

IT 59277-89-3, Acyclovir 161363-19-5
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(binding mode prediction of cytochrome P 450 and thymidine kinase protein-ligand complexes by consideration of water and rescoring in automated docking)

RN 59277-89-3 HCAPLUS
CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]- (CA INDEX NAME)



RN 161363-19-5 HCAPLUS
CN 6H-Purin-6-one, 1,9-dihydro-9-(4-hydroxybutyl)-2-(phenylamino)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:457254 HCAPLUS <<LOGINID::20070503>>
DOCUMENT NUMBER: 135:207324
TITLE: The rational of catalytic activity of herpes simplex virus thymidine kinase. A combined biochemical and quantum chemical study
AUTHOR(S): Sulpizi, Marialore; Schelling, Pierre; Folkers, Gerd; Carloni, Paolo; Scapozza, Leonardo
CORPORATE SOURCE: International School Advanced Studies, Scuola Internazionale Superiore Studi Aranzati, Trieste, 34013, Italy
SOURCE: Journal of Biological Chemistry (2001), 276(24), 21692-21697
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Most antiherpes therapies exploit the large substrate acceptance of herpes simplex virus type 1 thymidine kinase (TK HSV1) relative to the human isoenzyme. The enzyme selectively phosphosphorylates nucleoside analogs that can either inhibit viral DNA polymerase or cause toxic effects when incorporated into viral DNA. To relate structural properties of TKHSV1 ligands to their chemical reactivity we have carried out ab initio quantum chemical calcns. withing the d. functional theory framework in combination with biochem. studies. Calcns. have focused on a set of ligands carrying a representative set of the large spectrum of sugar-mimicking moieties and for which structural information of the TKHSV1ligand complex is available. The κcat values of these ligands have been measured under the same exptl. conditions using an UV spectrophotometric assay. The calcns. point to the crucial role of elec. dipole moment of ligands and its interaction with the neg. charged residue Glu225. A striking correlation is found between the energetics associated with this interaction and the κcat values measured under homogeneous conditions. This finding uncovers a fundamental aspect of the mechanism governing substrate diversity and

catalytic turnover and thus represents a significant step toward the rational design of novel and powerful prodrugs for antiviral and TKHSV1-linked suicide gene therapies.

IT 59277-89-3, Aciclovir 161363-19-5
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(biochem. and quantum chemical study of nucleoside analogs interaction with herpes simplex virus thymidine kinase)

RN 59277-89-3 HCAPLUS
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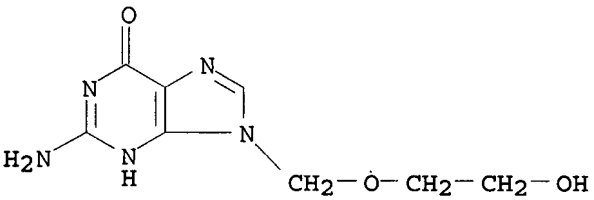

RN 161363-19-5 HCAPLUS
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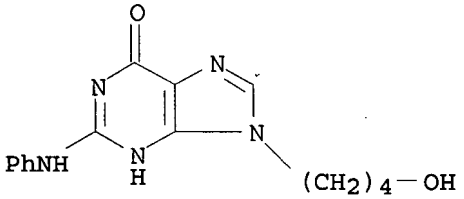

REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:60517 HCAPLUS <<LOGINID::20070503>>
DOCUMENT NUMBER: 130:293191
TITLE: Structure to 1.9 A resolution of a complex with herpes simplex virus type-1 thymidine kinase of a novel, non-substrate inhibitor: X-ray crystallographic comparison with binding of aciclovir
AUTHOR(S): Bennett, Matthew S.; Wien, Frank; Champness, John N.; Batuwangala, Thilina; Rutherford, Thomas; Summers, William C.; Sun, Hongmao; Wright, George; Sanderson, Mark R.
CORPORATE SOURCE: Randall Institute, Division of Biomedical Sciences, King's College, London, WC2B 5RL, UK
SOURCE: FEBS Letters (1999), 443(2), 121-125
CODEN: FEBLAL; ISSN: 0014-5793
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Treatment of herpes infections with nucleoside analogs requires as an initial step the activation of the compds. by thymidine kinase. As an aid to developing more effective chemotherapy, both for treatment of recurrent herpes infection and in gene therapy systems where thymidine kinase is

expressed, two high-resolution X-ray structures of thymidine kinase have been compared: one with the relatively poor substrate aciclovir (Zovirax), the other with a synthetic inhibitor having an N2-substituted guanine (HBPG; 9-(4-hydroxybutyl)-N2-phenylguanine). Both compds. have similar binding modes in spite of their size difference and apparently distinct ligand properties.

IT 59277-89-3D, Aciclovir, thymidine kinase complexes
161363-19-5D, thymidine kinase complexes
RL: PRP (Properties)
(crystal structure to 1.9 A resolution of a complex with herpes simplex virus type-1 thymidine kinase of a novel, non-substrate inhibitor and comparison with binding of aciclovir)

RN 59277-89-3 HCAPLUS
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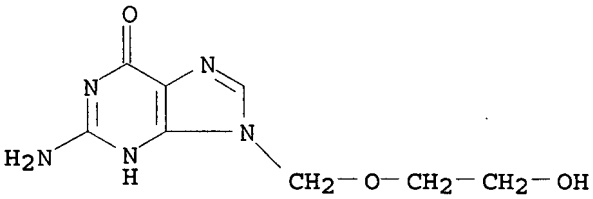

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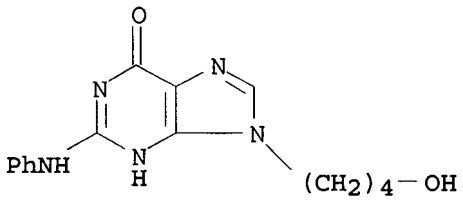

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FILE 'HCAPLUS' ENTERED AT 11:37:07 ON 03 MAY 2007

FILE 'REGISTRY' ENTERED AT 11:37:33 ON 03 MAY 2007
L1 1 S 161363-19-5/RN

FILE 'CHEMCATS' ENTERED AT 11:37:59 ON 03 MAY 2007
SET LIN 80
L2 0 S L1

FILE 'REGISTRY' ENTERED AT 11:38:09 ON 03 MAY 2007

FILE 'HCAPLUS' ENTERED AT 11:38:36 ON 03 MAY 2007
L3 11 S L1

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     FILE 'STNGUIDE' ENTERED AT 11:38:44 ON 03 MAY 2007

     FILE 'HCAPLUS' ENTERED AT 11:39:06 ON 03 MAY 2007
                E "161363-19-5"/BI,RN 25
L4             11 S E3 OR E5 OR E6
L5              0 S L4 NOT L3

     FILE 'STNGUIDE' ENTERED AT 11:40:03 ON 03 MAY 2007

     FILE 'HCAPLUS' ENTERED AT 11:42:16 ON 03 MAY 2007
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L6            648 S E3 OR E5 OR E6 OR E7
                E "4428-95-9"/BI,RN 25
L7           1041 S E3 OR E5 OR E6 OR E7
                E "59277-89-3"/BI,RN 25
L8           3560 S E3 OR E5 OR E6 OR E7
                E "66341-16-0"/BI,RN 25
L9             68 S E3 OR E5 OR E6 OR E7
                E "82410-32-0"/BI,RN 25
L10          3177 S E3 OR E5 OR E6 OR E7
                E "86761-39-9"/BI,RN 25
L11            22 S E3 OR E5 OR E6
                E "104227-87-4"/BI,RN 25
L12           544 S E3 OR E5 OR E6 OR E7
                E "161363-19-5"/BI,RN 25
L13            11 S E3 OR E5 OR E6
                E "113852-37-2"/BI,RN 25
L14           687 S E3 OR E5 OR E6 OR E7
                E "106941-25-7"/BI,RN 25
L15           648 S E3 OR E5 OR E6 OR E7
L16             1 S L4 AND L6
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=> s l21 not l16
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L23             3 L4 AND L10

=> s l23 not l16
L24             2 L23 NOT L16

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L24  ANSWER 1 OF 2  HCAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:         2005:134376  HCAPLUS <<LOGINID::20070503>>
DOCUMENT NUMBER:          142:366752
TITLE:                    Binding Mode Prediction of Cytochrome P450 and
                          Thymidine Kinase Protein-Ligand Complexes by
                          Consideration of Water and Rescoring in Automated
                          Docking
AUTHOR(S):                de Graaf, Chris; Pospisil, Pavel; Pos, Wouter;
                          Folkers, Gerd; Vermeulen, Nico P. E.
CORPORATE SOURCE:         Leiden/Amsterdam Center for Drug Research, Division of
                          Molecular Toxicology, Vrije Universiteit Amsterdam,
                          Amsterdam, 1081 HV, Neth.
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SOURCE: Journal of Medicinal Chemistry (2005), 48(7), 2308-2318
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The popular docking programs AutoDock, FlexX, and GOLD were used to predict binding modes of ligands in crystallog. complexes including x-ray water mols. or computationally predicted water mols. Isoenzymes of two different enzyme systems were used, namely cytochromes P 450 (n = 19) and thymidine kinases (n = 19) and three different "water" scenarios: i.e., docking (i) into water-free active sites, (ii) into active sites containing crystallog. water mols., and (iii) into active sites containing water mols. predicted by a novel approach based on the program GRID. Docking accuracies were determined in terms of the root-mean-square deviation (RMSD) accuracy and, newly defined, in terms of the ligand catalytic site prediction (CSP) accuracy. Consideration of both x-ray and predicted water mols. and the subsequent pooling and rescoring of all solns. (generated by all three docking programs) with the SCORE scoring function significantly improved the quality of prediction of the binding modes both in terms of RMSD and CSP accuracy.

IT 82410-32-0, Ganciclovir 161363-19-5
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(binding mode prediction of cytochrome P 450 and thymidine kinase protein-ligand complexes by consideration of water and rescoring in automated docking)

RN 82410-32-0 HCAPLUS
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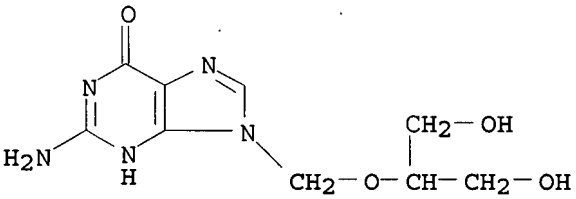
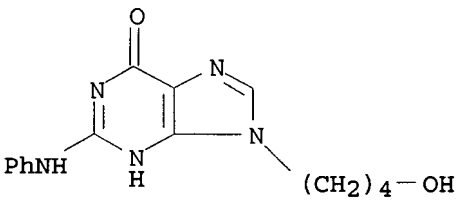


RN 161363-19-5 HCAPLUS
CN 6H-Purin-6-one, 1,9-dihydro-9-(4-hydroxybutyl)-2-(phenylamino)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:457254 HCAPLUS <<LOGINID::20070503>>
DOCUMENT NUMBER: 135:207324

TITLE: The rational of catalytic activity of herpes simplex virus thymidine kinase. A combined biochemical and quantum chemical study

AUTHOR(S): Sulpizi, Marialore; Schelling, Pierre; Folkers, Gerd; Carloni, Paolo; Scapozza, Leonardo

CORPORATE SOURCE: International School Advanced Studies, Scuola Internazionale Superiore Studi Aranzati, Trieste, 34013, Italy

SOURCE: Journal of Biological Chemistry (2001), 276(24), 21692-21697
CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

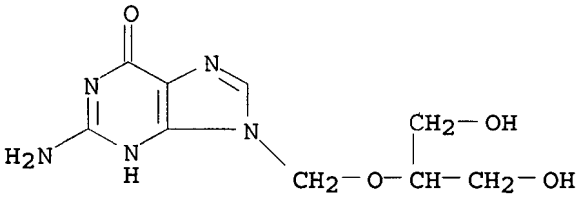
LANGUAGE: English

AB Most antiherpes therapies exploit the large substrate acceptance of herpes simplex virus type 1 thymidine kinase (TK HSV1) relative to the human isoenzyme. The enzyme selectively phosphosphorylates nucleoside analogs that can either inhibit viral DNA polymerase or cause toxic effects when incorporated into viral DNA. To relate structural properties of TKHSV1 ligands to their chemical reactivity we have carried out ab initio quantum chemical calcns. withing the d. functional theory framework in combination with biochem. studies. Calcns. have focused on a set of ligands carrying a representative set of the large spectrum of sugar-mimicking moieties and for which structural information of the TKHSV1ligand complex is available. The κcat values of these ligands have been measured under the same exptl. conditions using an UV spectrophotometric assay. The calcns. point to the crucial role of elec. dipole moment of ligands and its interaction with the neg. charged residue Glu225. A striking correlation is found between the energetics associated with this interaction and the κcat values measured under homogeneous conditions. This finding uncovers a fundamental aspect of the mechanism governing substrate diversity and catalytic turnover and thus represents a significant step toward the rational design of novel and powerful prodrugs for antiviral and TKHSV1-linked suicide gene therapies.

IT 82410-32-0, Ganciclovir 161363-19-5
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(biochem. and quantum chemical study of nucleoside analogs interaction with herpes simplex virus thymidine kinase)

RN 82410-32-0 HCAPLUS

CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]- (CA INDEX NAME)



RN 161363-19-5 HCAPLUS

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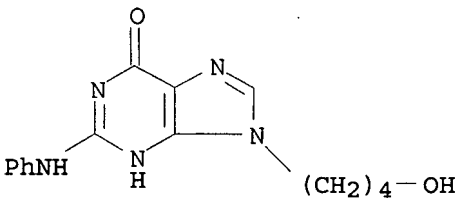

REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L1             1 S 161363-19-5/RN

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                SET LIN 80
L2             0 S L1

     FILE 'REGISTRY' ENTERED AT 11:38:09 ON 03 MAY 2007

     FILE 'HCAPLUS' ENTERED AT 11:38:36 ON 03 MAY 2007
L3            11 S L1

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     FILE 'HCAPLUS' ENTERED AT 11:39:06 ON 03 MAY 2007
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L4            11 S E3 OR E5 OR E6
L5             0 S L4 NOT L3

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L6           648 S E3 OR E5 OR E6 OR E7
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L7          1041 S E3 OR E5 OR E6 OR E7
                E "59277-89-3"/BI,RN 25
L8          3560 S E3 OR E5 OR E6 OR E7
                E "66341-16-0"/BI,RN 25
L9            68 S E3 OR E5 OR E6 OR E7
                E "82410-32-0"/BI,RN 25
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L11           22 S E3 OR E5 OR E6
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L13           11 S E3 OR E5 OR E6
                E "113852-37-2"/BI,RN 25
L14          687 S E3 OR E5 OR E6 OR E7
                E "106941-25-7"/BI,RN 25
L15          648 S E3 OR E5 OR E6 OR E7
L16            1 S L4 AND L6
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 NEWS  4  JAN 16  IPC version 2007.01 thesaurus available on STN
 NEWS  5  JAN 16  WPIDS/WPINDEX/WPIX enhanced with IPC 8 reclassification data
 NEWS  6  JAN 22  CA/CAplus updated with revised CAS roles
 NEWS  7  JAN 22  CA/CAplus enhanced with patent applications from India
 NEWS  8  JAN 29  PHAR reloaded with new search and display fields
 NEWS  9  JAN 29  CAS Registry Number crossover limit increased to 300,000 in
                  multiple databases
 NEWS 10  FEB 15  PATDPASPC enhanced with Drug Approval numbers
 NEWS 11  FEB 15  RUSSIAPAT enhanced with pre-1994 records
 NEWS 12  FEB 23  KOREAPAT enhanced with IPC 8 features and functionality
 NEWS 13  FEB 26  MEDLINE reloaded with enhancements
 NEWS 14  FEB 26  EMBASE enhanced with Clinical Trial Number field
 NEWS 15  FEB 26  TOXCENTER enhanced with reloaded MEDLINE
 NEWS 16  FEB 26  IFICDB/IFIPAT/IFIUDB reloaded with enhancements
 NEWS 17  FEB 26  CAS Registry Number crossover limit increased from 10,000
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 NEWS 18  MAR 15  WPIDS/WPIX enhanced with new FRAGHITSTR display format
 NEWS 19  MAR 16  CASREACT coverage extended
 NEWS 20  MAR 20  MARPAT now updated daily
 NEWS 21  MAR 22  LWPI reloaded
 NEWS 22  MAR 30  RDISCLOSURE reloaded with enhancements
 NEWS 23  APR 02  JICST-EPLUS removed from database clusters and STN
 NEWS 24  APR 30  GENBANK reloaded and enhanced with Genome Project ID field
 NEWS 25  APR 30  CHEMCATS enhanced with 1.2 million new records
 NEWS 26  APR 30  CA/CAplus enhanced with 1870-1889 U.S. patent records
 NEWS 27  APR 30  INPADOC replaced by INPADOCDB on STN
 NEWS 28  MAY 01  New CAS web site launched

 NEWS EXPRESS  NOVEMBER 10 CURRENT WINDOWS VERSION IS V8.01c, CURRENT
               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
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E22	1	86761-49-1/BI
E23	1	86761-49-1P/BI
E24	1	86761-50-4/BI
E25	1	86761-50-4P/BI

=> S E3 OR E5 OR E6
22 86761-39-9/BI

```
             1 86761-39-9D/BI
             5 86761-39-9P/BI
L1          22 86761-39-9/BI OR 86761-39-9D/BI OR 86761-39-9P/BI

=> E "104227-87-4"/BI,RN 25
E1          34     104227-86-3/BI
E2          17     104227-86-3P/BI
E3         544 --> 104227-87-4/BI
E4           0     104227-87-4/RN
E5          17     104227-87-4D/BI
E6           3     104227-87-4DP/BI
E7          45     104227-87-4P/BI
E8          12     104227-88-5/BI
E9           6     104227-88-5P/BI
E10          8     104227-89-6/BI
E11          8     104227-89-6P/BI
E12          5     104227-90-9/BI
E13          5     104227-90-9P/BI
E14          1     104227-91-0/BI
E15          1     104227-91-0P/BI
E16          1     104227-92-1/BI
E17          1     104227-92-1P/BI
E18          4     104227-93-2/BI
E19          4     104227-93-2P/BI
E20          4     104227-94-3/BI
E21          4     104227-94-3P/BI
E22          4     104227-95-4/BI
E23          4     104227-95-4P/BI
E24          3     104227-96-5/BI
E25          3     104227-96-5P/BI

=> E "104227-87-4"/BI,RN 25
E1          34     104227-86-3/BI
E2          17     104227-86-3P/BI
E3         544 --> 104227-87-4/BI
E4           0     104227-87-4/RN
E5          17     104227-87-4D/BI
E6           3     104227-87-4DP/BI
E7          45     104227-87-4P/BI
E8          12     104227-88-5/BI
E9           6     104227-88-5P/BI
E10          8     104227-89-6/BI
E11          8     104227-89-6P/BI
E12          5     104227-90-9/BI
E13          5     104227-90-9P/BI
E14          1     104227-91-0/BI
E15          1     104227-91-0P/BI
E16          1     104227-92-1/BI
E17          1     104227-92-1P/BI
E18          4     104227-93-2/BI
E19          4     104227-93-2P/BI
E20          4     104227-94-3/BI
E21          4     104227-94-3P/BI
E22          4     104227-95-4/BI
E23          4     104227-95-4P/BI
E24          3     104227-96-5/BI
E25          3     104227-96-5P/BI

=> S E3 OR E5 OR E6 OR E7
           544 104227-87-4/BI
            17 104227-87-4D/BI
             3 104227-87-4DP/BI
            45 104227-87-4P/BI
```

```
L2          544 104227-87-4/BI OR 104227-87-4D/BI OR 104227-87-4DP/BI OR 104227-87-4P/BI

=> E "161363-19-5"/BI,RN 25
E1            2     161363-18-4/BI
E2            2     161363-18-4P/BI
E3           11 --> 161363-19-5/BI
E4            0     161363-19-5/RN
E5            1     161363-19-5D/BI
E6            3     161363-19-5P/BI
E7            3     161363-20-8/BI
E8            3     161363-20-8P/BI
E9            3     161363-21-9/BI
E10           1     161363-21-9P/BI
E11           1     161363-22-0/BI
E12           1     161363-22-0P/BI
E13           3     161363-23-1/BI
E14           3     161363-23-1P/BI
E15           3     161363-24-2/BI
E16           2     161363-24-2P/BI
E17           3     161363-25-3/BI
E18           1     161363-25-3P/BI
E19           3     161363-26-4/BI
E20           3     161363-26-4P/BI
E21           3     161363-27-5/BI
E22           3     161363-27-5P/BI
E23           1     161363-28-6/BI
E24           1     161363-28-6P/BI
E25           1     161363-29-7/BI

=> S E3 OR E5 OR E6
             11 161363-19-5/BI
              1 161363-19-5D/BI
              3 161363-19-5P/BI
L3           11 161363-19-5/BI OR 161363-19-5D/BI OR 161363-19-5P/BI

=> E "113852-37-2"/BI,RN 25
E1            9     113852-36-1/BI
E2            4     113852-36-1P/BI
E3          687 --> 113852-37-2/BI
E4            0     113852-37-2/RN
E5           28     113852-37-2D/BI
E6            8     113852-37-2DP/BI
E7           27     113852-37-2P/BI
E8            8     113852-38-3/BI
E9            2     113852-38-3P/BI
E10           3     113852-39-4/BI
E11           1     113852-39-4P/BI
E12           4     113852-40-7/BI
E13           3     113852-40-7P/BI
E14         100     113852-41-8/BI
E15           1     113852-41-8D/BI
E16           9     113852-41-8P/BI
E17          16     113852-42-9/BI
E18           7     113852-42-9P/BI
E19           7     113852-43-0/BI
E20           2     113852-43-0P/BI
E21           3     113852-44-1/BI
E22           1     113852-44-1P/BI
E23           5     113852-46-3/BI
E24           1     113852-46-3P/BI
E25           2     113852-47-4/BI

=> S E3 OR E5 OR E6 OR E7
```

```
            687 113852-37-2/BI
             28 113852-37-2D/BI
              8 113852-37-2DP/BI
             27 113852-37-2P/BI
L4          687 113852-37-2/BI OR 113852-37-2D/BI OR 113852-37-2DP/BI OR 113852-37-2P/BI

=> E "106941-25-7"/BI,RN 25
E1            2     106941-23-5P/BI
E2            1     106941-24-6/BI
E3          648 --> 106941-25-7/BI
E4            0     106941-25-7/RN
E5           27     106941-25-7D/BI
E6            8     106941-25-7DP/BI
E7           42     106941-25-7P/BI
E8            1     106941-26-8/BI
E9            3     106941-27-9/BI
E10           1     106941-28-0/BI
E11           1     106941-28-0P/BI
E12           1     106941-29-1/BI
E13           1     106941-29-1P/BI
E14           1     106941-30-4/BI
E15           1     106941-30-4P/BI
E16           1     106941-31-5/BI
E17           1     106941-31-5P/BI
E18           1     106941-32-6/BI
E19           1     106941-32-6P/BI
E20           4     106941-33-7/BI
E21           3     106941-33-7P/BI
E22           1     106941-34-8/BI
E23           2     106941-35-9/BI
E24           1     106941-35-9P/BI
E25           2     106941-36-0/BI

=> S E3 OR E5 OR E6 OR E7
            648 106941-25-7/BI
             27 106941-25-7D/BI
              8 106941-25-7DP/BI
             42 106941-25-7P/BI
L5          648 106941-25-7/BI OR 106941-25-7D/BI OR 106941-25-7DP/BI OR 106941-25-7P/BI

=>  his
HIS IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> d his

     (FILE 'HOME' ENTERED AT 14:27:11 ON 03 MAY 2007)

     FILE 'HCAPLUS' ENTERED AT 14:27:17 ON 03 MAY 2007
                E "86761-39-9"/BI,RN 25
L1           22 S E3 OR E5 OR E6
                E "104227-87-4"/BI,RN 25
                E "104227-87-4"/BI,RN 25
L2          544 S E3 OR E5 OR E6 OR E7
                E "161363-19-5"/BI,RN 25
L3           11 S E3 OR E5 OR E6
                E "113852-37-2"/BI,RN 25
L4          687 S E3 OR E5 OR E6 OR E7
                E "106941-25-7"/BI,RN 25
L5          648 S E3 OR E5 OR E6 OR E7
```

10767019>05/05/2007

=> s l1-l5
L6 1634 (L1 OR L2 OR L3 OR L4 OR L5)

=> s l3 and (l1 or l2 or l4 or l5)
L7 1 L3 AND (L1 OR L2 OR L4 OR L5)

=> d ti

L7 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2007 ACS on STN
TI Novel antiherpes drug combinations of Herpes simplex virus thymidine kinase inhibitors and antiherpes substances

=> fil stng
COST IN U.S. DOLLARS SINCE FILE ENTRY 10.74 TOTAL SESSION 10.95
FULL ESTIMATED COST

FILE 'STNGUIDE' ENTERED AT 14:29:43 ON 03 MAY 2007
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=> logoff
ALL L# QUERIES AND ANSWER SETS ARE DELETED AT LOGOFF
LOGOFF? (Y)/N/HOLD:y
COST IN U.S. DOLLARS SINCE FILE ENTRY 0.06 TOTAL SESSION 11.01
FULL ESTIMATED COST

STN INTERNATIONAL LOGOFF AT 14:30:11 ON 03 MAY 2007

Connecting via Winsock to STN

Welcome to STN International! Enter x:x

LOGINID:ssptarpi1623

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS	1		Web Page URLs for STN Seminar Schedule - N. America
NEWS	2	JAN 08	CHEMLIST enhanced with New Zealand Inventory of Chemicals
NEWS	3	JAN 16	CA/CAplus Company Name Thesaurus enhanced and reloaded
NEWS	4	JAN 16	IPC version 2007.01 thesaurus available on STN
NEWS	5	JAN 16	WPIDS/WPINDEX/WPIX enhanced with IPC 8 reclassification data
NEWS	6	JAN 22	CA/CAplus updated with revised CAS roles
NEWS	7	JAN 22	CA/CAplus enhanced with patent applications from India
NEWS	8	JAN 29	PHAR reloaded with new search and display fields
NEWS	9	JAN 29	CAS Registry Number crossover limit increased to 300,000 in multiple databases
NEWS	10	FEB 15	PATDPASPC enhanced with Drug Approval numbers

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 NEWS 11   FEB 15  RUSSIAPAT enhanced with pre-1994 records
 NEWS 12   FEB 23  KOREAPAT enhanced with IPC 8 features and functionality
 NEWS 13   FEB 26  MEDLINE reloaded with enhancements
 NEWS 14   FEB 26  EMBASE enhanced with Clinical Trial Number field
 NEWS 15   FEB 26  TOXCENTER enhanced with reloaded MEDLINE
 NEWS 16   FEB 26  IFICDB/IFIPAT/IFIUDB reloaded with enhancements
 NEWS 17   FEB 26  CAS Registry Number crossover limit increased from 10,000
                   to 300,000 in multiple databases
 NEWS 18   MAR 15  WPIDS/WPIX enhanced with new FRAGHITSTR display format
 NEWS 19   MAR 16  CASREACT coverage extended
 NEWS 20   MAR 20  MARPAT now updated daily
 NEWS 21   MAR 22  LWPI reloaded
 NEWS 22   MAR 30  RDISCLOSURE reloaded with enhancements
 NEWS 23   APR 02  JICST-EPLUS removed from database clusters and STN
 NEWS 24   APR 30  GENBANK reloaded and enhanced with Genome Project ID field
 NEWS 25   APR 30  CHEMCATS enhanced with 1.2 million new records
 NEWS 26   APR 30  CA/CAplus enhanced with 1870-1889 U.S. patent records
 NEWS 27   APR 30  INPADOC replaced by INPADOCDB on STN
 NEWS 28   MAY 01  New CAS web site launched

 NEWS EXPRESS  NOVEMBER 10 CURRENT WINDOWS VERSION IS V8.01c, CURRENT
               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 25 SEPTEMBER 2006.

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=> fil hcaplus
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                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       0.21       0.21

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10767019>05/05/2007

FILE LAST UPDATED: 1 May 2007 (20070501/ED)

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```
=> E WRIGHT G/AU 25
E1            1     WRIGHT FRITZ M/AU
E2            3     WRIGHT FULTON JR/AU
E3           76 --> WRIGHT G/AU
E4           53     WRIGHT G A/AU
E5            4     WRIGHT G A E/AU
E6            1     WRIGHT G ALBERT/AU
E7           13     WRIGHT G B/AU
E8            8     WRIGHT G C/AU
E9            9     WRIGHT G D/AU
E10           1     WRIGHT G D S/AU
E11          17     WRIGHT G E/AU
E12          21     WRIGHT G F/AU
E13           3     WRIGHT G F JR/AU
E14           6     WRIGHT G G/AU
E15           1     WRIGHT G G H/AU
E16           7     WRIGHT G H/AU
E17          43     WRIGHT G J/AU
E18          54     WRIGHT G L/AU
E19           9     WRIGHT G L JR/AU
E20          17     WRIGHT G M/AU
E21           3     WRIGHT G MCN/AU
E22           1     WRIGHT G N/AU
E23           7     WRIGHT G P/AU
E24          31     WRIGHT G PAYLING/AU
E25          11     WRIGHT G R/AU

=> E 25
E26           1     WRIGHT G R G/AU
E27          30     WRIGHT G S/AU
E28          31     WRIGHT G T/AU
E29          20     WRIGHT G W/AU
E30           1     WRIGHT G WAYNE/AU
E31           2     WRIGHT G Z/AU
E32           6     WRIGHT GABRIELA/AU
E33           1     WRIGHT GABRIELA M/AU
E34           1     WRIGHT GABRIELA M J S/AU
E35           2     WRIGHT GABRIELLA/AU
E36           5     WRIGHT GAIL C/AU
E37           1     WRIGHT GAIL E/AU
E38           1     WRIGHT GAIL K/AU
E39           2     WRIGHT GAIL P/AU
E40           1     WRIGHT GAIL SHAW/AU
E41           5     WRIGHT GARCIA KIMBERLEY/AU
E42           2     WRIGHT GARDNER V/AU
E43          17     WRIGHT GARY/AU
E44          10     WRIGHT GARY A/AU
E45           1     WRIGHT GARY ALAN/AU
E46           1     WRIGHT GARY B/AU
E47           2     WRIGHT GARY C/AU
E48           1     WRIGHT GARY D/AU
E49           1     WRIGHT GARY J/AU
E50           3     WRIGHT GARY JOHN/AU

=> E 25
E51          22     WRIGHT GARY L/AU
E52           1     WRIGHT GARY LEE/AU
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E53           1     WRIGHT GARY LESLIE/AU
E54          20     WRIGHT GAVIN/AU
E55          10     WRIGHT GAVIN J/AU
E56           1     WRIGHT GENE A/AU
E57           6     WRIGHT GENESIS P/AU
E58           1     WRIGHT GEO/AU
E59           4     WRIGHT GEO C/AU
E60          53     WRIGHT GEO F/AU
E61           8     WRIGHT GEO G/AU
E62           1     WRIGHT GEO G JR/AU
E63           1     WRIGHT GEO H/AU
E64           1     WRIGHT GEO J/AU
E65           2     WRIGHT GEO M/AU
E66           1     WRIGHT GEO T/AU
E67           5     WRIGHT GEO W/AU
E68           3     WRIGHT GEOFF/AU
E69           1     WRIGHT GEOFF C/AU
E70           1     WRIGHT GEOFF R/AU
E71           3     WRIGHT GEOFFREY/AU
E72           1     WRIGHT GEOFFREY A/AU
E73           1     WRIGHT GEOFFREY ANTHONY/AU
E74           1     WRIGHT GEOFFREY B/AU
E75           4     WRIGHT GEOFFREY R/AU

=> E 25
E76           1     WRIGHT GEOFFRY R/AU
E77          46     WRIGHT GEORGE/AU
E78           2     WRIGHT GEORGE A/AU
E79          81     WRIGHT GEORGE B/AU
E80           7     WRIGHT GEORGE BUFORD/AU
E81          57     WRIGHT GEORGE C/AU
E82           3     WRIGHT GEORGE C JR/AU
E83           4     WRIGHT GEORGE CARLIN/AU
E84           1     WRIGHT GEORGE D/AU
E85         105     WRIGHT GEORGE E/AU
E86           4     WRIGHT GEORGE EDWARD/AU
E87         150     WRIGHT GEORGE F/AU
E88           1     WRIGHT GEORGE F JR/AU
E89          15     WRIGHT GEORGE G/AU
E90           2     WRIGHT GEORGE GREEN/AU
E91           1     WRIGHT GEORGE H/AU
E92           4     WRIGHT GEORGE HENRY/AU
E93           1     WRIGHT GEORGE HODGSON/AU
E94          22     WRIGHT GEORGE J/AU
E95           5     WRIGHT GEORGE JOSEPH/AU
E96           5     WRIGHT GEORGE L/AU
E97          65     WRIGHT GEORGE L JR/AU
E98           3     WRIGHT GEORGE LEONARD JR/AU
E99           5     WRIGHT GEORGE M/AU
E100          1     WRIGHT GEORGE MARTIN/AU

=> E 25
E101          4     WRIGHT GEORGE T/AU
E102          1     WRIGHT GEORGE TODD/AU
E103         13     WRIGHT GEORGE W/AU
E104          2     WRIGHT GEORGE WAYNE/AU
E105          1     WRIGHT GEORGE WILBUR/AU
E106          1     WRIGHT GEORGE WILLIAM/AU
E107          3     WRIGHT GEORGES/AU
E108          2     WRIGHT GEORGIA E/AU
E109          3     WRIGHT GERALD D/AU
E110          2     WRIGHT GERALDINE/AU
E111         10     WRIGHT GERALDINE A/AU
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E112          4      WRIGHT GERARD/AU
E113         91      WRIGHT GERARD D/AU
E114          2      WRIGHT GERRY/AU
E115          1      WRIGHT GILES/AU
E116          5      WRIGHT GILLIAN/AU
E117         11      WRIGHT GILLIAN S/AU
E118          1      WRIGHT GLEN LAWRENCE/AU
E119         36      WRIGHT GLENDA M/AU
E120          1      WRIGHT GLENDA MARY/AU
E121          3      WRIGHT GLENFORD/AU
E122          1      WRIGHT GLENN A/AU
E123          7      WRIGHT GLENN C/AU
E124          1      WRIGHT GLENN E/AU
E125          1      WRIGHT GLENN T/AU

=> E WRIGHT GEORGE/AU 25
E1            4      WRIGHT GEOFFREY R/AU
E2            1      WRIGHT GEOFFRY R/AU
E3           46  --> WRIGHT GEORGE/AU
E4            2      WRIGHT GEORGE A/AU
E5           81      WRIGHT GEORGE B/AU
E6            7      WRIGHT GEORGE BUFORD/AU
E7           57      WRIGHT GEORGE C/AU
E8            3      WRIGHT GEORGE C JR/AU
E9            4      WRIGHT GEORGE CARLIN/AU
E10           1      WRIGHT GEORGE D/AU
E11         105      WRIGHT GEORGE E/AU
E12           4      WRIGHT GEORGE EDWARD/AU
E13         150      WRIGHT GEORGE F/AU
E14           1      WRIGHT GEORGE F JR/AU
E15          15      WRIGHT GEORGE G/AU
E16           2      WRIGHT GEORGE GREEN/AU
E17           1      WRIGHT GEORGE H/AU
E18           4      WRIGHT GEORGE HENRY/AU
E19           1      WRIGHT GEORGE HODGSON/AU
E20          22      WRIGHT GEORGE J/AU
E21           5      WRIGHT GEORGE JOSEPH/AU
E22           5      WRIGHT GEORGE L/AU
E23          65      WRIGHT GEORGE L JR/AU
E24           3      WRIGHT GEORGE LEONARD JR/AU
E25           5      WRIGHT GEORGE M/AU

=> S (E3 OR E4 OR E5 OR E6 OR E7 OR E8 OR E9 OR E10 OR E11 OR E12 OR E13 OR E14 OR E15 OR E16
OR E17 OR E18 OR E19 OR E20 OR E21 OR E22 OR E23 OR E24 OR E25)
            46 "WRIGHT GEORGE"/AU
             2 "WRIGHT GEORGE A"/AU
            81 "WRIGHT GEORGE B"/AU
             7 "WRIGHT GEORGE BUFORD"/AU
            57 "WRIGHT GEORGE C"/AU
             3 "WRIGHT GEORGE C JR"/AU
             4 "WRIGHT GEORGE CARLIN"/AU
             1 "WRIGHT GEORGE D"/AU
           105 "WRIGHT GEORGE E"/AU
             4 "WRIGHT GEORGE EDWARD"/AU
           150 "WRIGHT GEORGE F"/AU
             1 "WRIGHT GEORGE F JR"/AU
            15 "WRIGHT GEORGE G"/AU
             2 "WRIGHT GEORGE GREEN"/AU
             1 "WRIGHT GEORGE H"/AU
             4 "WRIGHT GEORGE HENRY"/AU
             1 "WRIGHT GEORGE HODGSON"/AU
            22 "WRIGHT GEORGE J"/AU
             5 "WRIGHT GEORGE JOSEPH"/AU
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```
             5 "WRIGHT GEORGE L"/AU
            65 "WRIGHT GEORGE L JR"/AU
             3 "WRIGHT GEORGE LEONARD JR"/AU
             5 "WRIGHT GEORGE M"/AU
L1         588 ("WRIGHT GEORGE"/AU OR "WRIGHT GEORGE A"/AU OR "WRIGHT GEORGE B"/AU OR "WRIGHT
GEORGE BUFORD"/AU OR "WRIGHT GEORGE C"/AU OR "WRIGHT GEORGE C JR"/AU OR "WRIGHT GEORGE
CARLIN"/AU OR "WRIGHT GEORGE D"/AU OR "WRIGHT GEORGE E"/AU OR "WRIGH
               T GEORGE EDWARD"/AU OR "WRIGHT GEORGE F"/AU OR "WRIGHT GEORGE F JR"/AU OR
"WRIGHT GEORGE G"/AU OR "WRIGHT GEORGE GREEN"/AU OR "WRIGHT GEORGE H"/AU OR "WRIGHT GEORGE
HENRY"/AU OR "WRIGHT GEORGE HODGSON"/AU OR "WRIGHT GEORGE J"/AU OR
              "WRIGHT GEORGE JOSEPH"/AU OR "WRIGHT GEORGE L"/AU OR "WRIGHT GEORGE L JR"/AU OR
"WRIGHT GEORGE LEONARD JR"/AU OR "WRIGHT GEORGE M"/AU)

=> E 25
E26          1     WRIGHT GEORGE MARTIN/AU
E27          4     WRIGHT GEORGE T/AU
E28          1     WRIGHT GEORGE TODD/AU
E29         13     WRIGHT GEORGE W/AU
E30          2     WRIGHT GEORGE WAYNE/AU
E31          1     WRIGHT GEORGE WILBUR/AU
E32          1     WRIGHT GEORGE WILLIAM/AU
E33          3     WRIGHT GEORGES/AU
E34          2     WRIGHT GEORGIA E/AU
E35          3     WRIGHT GERALD D/AU
E36          2     WRIGHT GERALDINE/AU
E37         10     WRIGHT GERALDINE A/AU
E38          4     WRIGHT GERARD/AU
E39         91     WRIGHT GERARD D/AU
E40          2     WRIGHT GERRY/AU
E41          1     WRIGHT GILES/AU
E42          5     WRIGHT GILLIAN/AU
E43         11     WRIGHT GILLIAN S/AU
E44          1     WRIGHT GLEN LAWRENCE/AU
E45         36     WRIGHT GLENDA M/AU
E46          1     WRIGHT GLENDA MARY/AU
E47          3     WRIGHT GLENFORD/AU
E48          1     WRIGHT GLENN A/AU
E49          7     WRIGHT GLENN C/AU
E50          1     WRIGHT GLENN E/AU

=> S (E26 OR E27 OR E28 OR E29 OR E30 OR E31 OR E32)
             1 "WRIGHT GEORGE MARTIN"/AU
             4 "WRIGHT GEORGE T"/AU
             1 "WRIGHT GEORGE TODD"/AU
            13 "WRIGHT GEORGE W"/AU
             2 "WRIGHT GEORGE WAYNE"/AU
             1 "WRIGHT GEORGE WILBUR"/AU
             1 "WRIGHT GEORGE WILLIAM"/AU
L2          23 ("WRIGHT GEORGE MARTIN"/AU OR "WRIGHT GEORGE T"/AU OR "WRIGHT GEORGE TODD"/AU
OR "WRIGHT GEORGE W"/AU OR "WRIGHT GEORGE WAYNE"/AU OR "WRIGHT GEORGE WILBUR"/AU OR "WRIGHT
GEORGE WILLIAM"/AU)

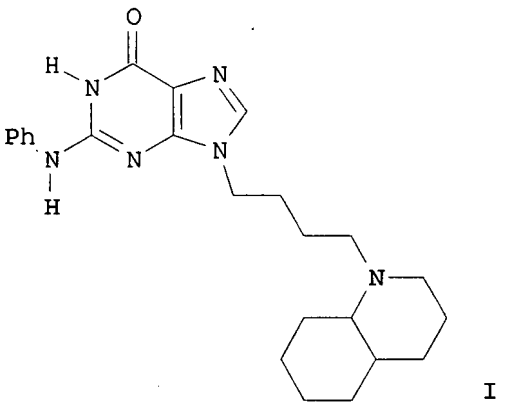
=> s l1 or l2
L3          611 L1 OR L2

=> s l3 and herpes
         26188 HERPES
L4           19 L3 AND HERPES

=> d l4 ibib abs

L4   ANSWER 1 OF 19  HCAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:        2005:398777  HCAPLUS <<LOGINID::20070503>>
```

DOCUMENT NUMBER: 143:97319
TITLE: Inhibition of Herpes Simplex Virus Thymidine Kinases by 2-Phenylamino-6-oxopurines and Related Compounds: Structure-Activity Relationships and Antiherpetic Activity in Vivo
AUTHOR(S): Manikowski, Andrzej; Verri, Annalisa; Lossani, Andrea; Gebhardt, Bryan M.; Gambino, Joseph; Focher, Federico; Spadari, Silvio; Wright, George E.
CORPORATE SOURCE: GLSynthesis Inc., Worcester, MA, 01605, USA
SOURCE: Journal of Medicinal Chemistry (2005), 48(11), 3919-3929
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 143:97319
GI



I

AB Derivs. of the herpes simplex thymidine kinase inhibitor HBPG [2-phenylamino-9-(4-hydroxybutyl)-6-oxopurine] have been synthesized and tested for inhibitory activity against recombinant enzymes (TK) from herpes simplex types 1 and 2 (HSV-1, HSV-2). The compds. inhibited phosphorylation of [3H]thymidine by both enzymes, but potencies differed quant. from those of HBPG and were generally greater for HSV-2 than HSV-1 TKs. Changes in inhibitory potency were generally consistent with the inhibitor/substrate binding site structure based on published X-ray structures of HSV-1 TK. In particular, several 9-(4-aminobutyl) analogs with bulky tertiary amino substituents were among the most potent inhibitors. Variable substrate assays showed that the most potent compound, 2-phenylamino-9-[4-(1-decahydroquinolyl)butyl]-6-oxopurine (I·2 HCl), was a competitive inhibitor, with Ki values of 0.03 and 0.005 μM against HSV-1 and HSV-2 TKs, resp. The parent compound HBPG was uniquely active in viral infection models in mice, both against ocular HSV-2 reactivation and against HSV-1 and HSV-2 encephalitis. In assays lacking [3H]thymidine, HBPG was found to be an efficient substrate for the enzymes. The ability of the TKs to phosphorylate HBPG may relate to its antiherpetic activity in vivo.
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> s l4 and combinat?

```
        617320 COMBINAT?
L5           1 L4 AND COMBINAT?

=> d ti

L5   ANSWER 1 OF 1  HCAPLUS  COPYRIGHT 2007 ACS on STN
TI   Novel antiherpes drug combinations of Herpes simplex
     virus thymidine kinase inhibitors and antiherpes substances


=> d l4 ibib abs 2-5

L4   ANSWER 2 OF 19  HCAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:        2004:681513  HCAPLUS <<LOGINID::20070503>>
DOCUMENT NUMBER:         141:185078
TITLE:                   Novel antiherpes drug combinations of Herpes
                         simplex virus thymidine kinase inhibitors and
                         antiherpes substances
INVENTOR(S):             Wright, George E.
PATENT ASSIGNEE(S):      University of Massachusetts, USA
SOURCE:                  PCT Int. Appl., 22 pp.
                         CODEN: PIXXD2
DOCUMENT TYPE:           Patent
LANGUAGE:                English
FAMILY ACC. NUM. COUNT:  1
PATENT INFORMATION:

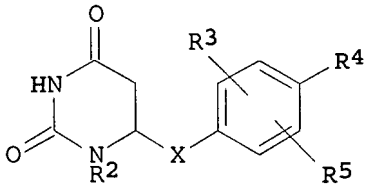
     PATENT NO.           KIND   DATE        APPLICATION NO.        DATE
     ---------------      ----   --------    --------------------   --------
     WO 2004069168         A2    20040819    WO 2004-US2427         20040129
     WO 2004069168         A3    20050915
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI
         RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE,
             BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU,
             MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN,
             GQ, GW, ML, MR, NE, SN, TD, TG
     CA 2514334            A1    20040819    CA 2004-2514334        20040129
     US 2004259832         A1    20041223    US 2004-767019         20040129
     EP 1594507            A2    20051116    EP 2004-706459         20040129
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
PRIORITY APPLN. INFO.:                   US 2003-443519P     P  20030129
                                         WO 2004-US2427      W  20040129
AB   Composition and methods are disclosed that include a synergistic combination of
     an inhibitor of Herpes simplex virus thymidine kinase, and an
     antiherpes substance.  The effect of combination of 2-phenylamino-9-(4-
     hydroxybutyl)-6-oxopurine and foscarnet against HSV2 encephalitis in mice
     was examined

L4   ANSWER 3 OF 19  HCAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:        2001:58588  HCAPLUS <<LOGINID::20070503>>
DOCUMENT NUMBER:         134:115965
TITLE:                   Preparation of uracil derivatives as inhibitors of
                         Herpes simplex virus uracil-DNA glycosylase
INVENTOR(S):             Wright, George E.
PATENT ASSIGNEE(S):      University of Massachusetts Medical Center, USA
SOURCE:                  U.S., 19 pp.
                         CODEN: USXXAM
DOCUMENT TYPE:           Patent
LANGUAGE:                English
```

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 6177437	B1	20010123	US 1999-388006		19990901
PRIORITY APPLN. INFO.:			US 1998-99274P	P	19980904

OTHER SOURCE(S): MARPAT 134:115965
GI



I

AB 6-Aromatic substituted uracil compds. I [X = O, NR1, CH2 and R1 = H, alkyl; R2 = H, alkyl, = (un)substituted Ph, alkoxyalkyl, etc.; R3, R5 = H, carboxamido, etc.; R4 = alkyl, alkenyl, alkoxy] were prepared Methods of treating Herpes simplex virus Type I and Type II recurrent infections and Herpes simplex virus Type I and Type II encephalitis in humans using the compds. and/or therapeutic compns. are investigated. E.g., a mixture of 6-chlorouracil and 4-decylaniline was heated to 200° to give 90% 6-(4-decylanilino)uracil.
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 19 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:34133 HCAPLUS <<LOGINID::20070503>>
DOCUMENT NUMBER: 132:302785
TITLE: Status of inhibitors of herpes simplex thymidine kinases
AUTHOR(S): Wright, George E.; Gambino, Joseph J.; Sun, Hongmao; Gebhardt, Bryan M.
CORPORATE SOURCE: GL Synthesis Inc, Shrewsbury, MA, 01545, USA
SOURCE: Current Opinion in Anti-Infective Investigational Drugs (1999), 1(5), 541-546
CODEN: COADFY; ISSN: 1464-8458
PUBLISHER: Current Drugs Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 23 refs. Determination of the crystal structures of complexes of herpes simplex virus type 1 thymidine kinase (HSV1 TK) with its substrates has provided a detailed picture of the active site and an understanding of the wide substrate range of the enzyme. The binding mode of a class of nonsubstrate inhibitors, exemplified by 9-(4-hydroxybutyl)-N2-phenylguanine (HBPG), has been revealed in the crystal structure of the TK:HBPG complex, allowing rational design of improved inhibitors. Further studies of the effect of HBPG in a murine model of HSV1 latency demonstrated the promise of TK inhibitors in preventing reactivation of herpetic diseases.
REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 19 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:371578 HCAPLUS <<LOGINID::20070503>>
DOCUMENT NUMBER: 131:164978

TITLE: Molecular Modeling and Synthesis of Inhibitors of Herpes Simplex Virus Type 1 Uracil-DNA Glycosylase
AUTHOR(S): Sun, Hongmao; Zhi, Chengxin; Wright, George E. ; Ubiali, Daniela; Pregnolato, Massimo; Verri, Annalisa; Focher, Federico; Spadari, Silvio
CORPORATE SOURCE: Department of Pharmacology and Molecular Toxicology, University of Massachusetts Medical Center, Worcester, MA, 01655, USA
SOURCE: Journal of Medicinal Chemistry (1999), 42(13), 2344-2350
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Properties of the first selective inhibitors of herpes simplex virus type 1 (HSV1) uracil-DNA glycosylase (UDG), an enzyme of DNA repair that has been proposed to be required for reactivation of the virus from latency, have been reported recently. 6-(4-Octylanilino)uracil (octAU) was the most potent inhibitor among a series of 6-(4-alkylanilino)uracils, acting in the micromolar range and without effect against human UDG. A 28.5-kDa catalytic fragment of HSV1 UDG has been crystallized in the presence of uracil, and the structure was recently solved. The coordinates of this structure were used in order to study interaction of inhibitors with the enzyme, and a model of binding between octAU and UDG was derived. Starting with the optimized model, the activity of several octAU analogs was predicted, and the values compared favorably with exptl. results found for the synthetic compds. Several hydrophilic derivs. were predicted and found to be active as UDG inhibitors. These compds. will be useful to determine if UDG, like the viral thymidine kinase, is required for reactivation of HSV1 from latency in nerve cells.

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> fil stng

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	30.09	30.30

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-3.90	-3.90

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FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Apr 27, 2007 (20070427/UP).

=> fil hcaplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.06	30.36

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CA SUBSCRIBER PRICE	0.00	-3.90

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10767019>05/05/2007

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FILE COVERS 1907 - 3 May 2007 VOL ISS
FILE LAST UPDATED: 2 May 2007 (20070502/ED)
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FILE COVERS 1907 - 3 May 2007 VOL 146 ISS 19
FILE LAST UPDATED: 1 May 2007 (20070501/ED)

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This file contains CAS Registry Numbers for easy and accurate

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        317402 "INFECTION"
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        255396 "SKIN"
         10347 "SKINS"
        261265 "SKIN"
                 ("SKIN" OR "SKINS")
        950309 "DISEASE"
        257327 "DISEASES"
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                 ("DISEASE" OR "DISEASES")
         32845 "SKIN, DISEASE"
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               E" (L) "HERPES")

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THERAPY" OR "E4           0     1     COMBINATIONS/CT" OR "E7        3888     9
COMBINATORIAL CHEMISTRY/CT" OR "E4           0     1     COMBINATIONS/CT"
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        116308 COMBINATIONS
        594825 COMBINATION
                 (COMBINATION OR COMBINATIONS)
        312210 THERAPY
         28032 THERAPIES
        327271 THERAPY
                 (THERAPY OR THERAPIES)
         11979 COMBINATION THERAPY
                 (COMBINATION(W)THERAPY)
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       5595846 "0"
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        504026 "COMBINATION"
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               TION/CT" OR "COMBINATION THERAPY" OR "E4            0      1
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             STRY/CT" OR "E4             0      1     COMBINATIONS/CT"

=> d his

     (FILE 'HOME' ENTERED AT 15:04:54 ON 03 MAY 2007)

     FILE 'HCAPLUS' ENTERED AT 15:04:59 ON 03 MAY 2007
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               E WRIGHT GEORGE/AU 25
L1           588 S (E3 OR E4 OR E5 OR E6 OR E7 OR E8 OR E9 OR E10 OR E11 OR E12
L2            23 S (E26 OR E27 OR E28 OR E29 OR E30 OR E31 OR E32)
L3           611 S L1 OR L2
L4            19 S L3 AND HERPES
L5             1 S L4 AND COMBINAT?

     FILE 'STNGUIDE' ENTERED AT 15:08:39 ON 03 MAY 2007

     FILE 'HCAPLUS' ENTERED AT 15:08:55 ON 03 MAY 2007
               E HERPES+ALL/CT
L6         26188 S (HERPES OR "HERPES" OR "INFECTION" (L) "HERPES" OR "SKIN, DIS
               E COMBINATION THERAPY+ALL/CT
L7         11982 S L6 AND COMBINATION THERAPY  OR "E1             0     1     COMB

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THERAPY" OR "E4             0     1     COMBINATIONS/CT")
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         28032 "THERAPIES"
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                 ("THERAPY" OR "THERAPIES")
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          6390 "E4"
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L8       11982 (COMBINATION THERAPY OR "E1            0     1     COMBINATION/CT
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              IONS/CT")

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        116308 COMBINATIONS
        594825 COMBINATION
                 (COMBINATION OR COMBINATIONS)
        312210 THERAPY
         28032 THERAPIES
        327271 THERAPY
                 (THERAPY OR THERAPIES)
L9       11979 COMBINATION THERAPY
                 (COMBINATION(W)THERAPY)

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L10        114 L9 AND L6

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        289515 KINASE
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L11         31 L10 AND KINASE

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           684 CIDOFOVIR
L12          0 L0 AND CIDOFOVIR

=> s l10 and cidofovir
            76 LL0
           684 CIDOFOVIR
L13          0 LL0 AND CIDOFOVIR

=> s l10 and cidofovir
           684 CIDOFOVIR
L14          5 L10 AND CIDOFOVIR

=> d l14 ibib abs 1-5

L14  ANSWER 1 OF 5  HCAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:         2007:217656  HCAPLUS <<LOGINID::20070503>>
DOCUMENT NUMBER:          146:350372
TITLE:                    Acyclic nucleoside phosphonates: Past, present and
                          future
AUTHOR(S):                De Clercq, E.
CORPORATE SOURCE:         Rega Institute for Medical Research, K.U. Leuven,
                          Louvain, B-3000, Belg.
SOURCE:                   Biochemical Pharmacology (2007), 73(7), 911-922
                          CODEN: BCPCA6; ISSN: 0006-2952
PUBLISHER:                Elsevier B.V.
DOCUMENT TYPE:            Journal; General Review
LANGUAGE:                 English
AB   A review.  Twenty years following the description of the broad-spectrum
     antiviral activity of S-9-(3-hydroxy-2-phosphonylmethoxypropyl)adenine the
```

acyclic nucleoside phosphonates have acquired a prominent therapeutic position: (i) cidofovir in the treatment of papilloma-, herpes-, adeno- and poxvirus infections, (ii) adefovir in the treatment of chronic hepatitis B virus (HBV) infections, and (iii) tenofovir in the treatment of human immunodeficiency virus (HIV) infections (AIDS). Although formally approved only for the treatment of human cytomegalovirus (HCMV) retinitis in AIDS patients, cidofovir has been used successfully in the treatment of various other DNA virus infections, particularly human papilloma virus (HPV)-associated lesions. Adefovir dipivoxil has become a standard therapy for HBV infections, especially when resistant to lamivudine. Tenofovir disoproxil fumarate (TDF) is the corner stone of the triple-drug (TDF, emtricitabine, and efavirenz) combination therapy for AIDS, and TDF, alone or combined with emtricitabine may in the future evolve to the standard therapy of hepatitis B. Guided by the results obtained with tenofovir in the prevention of parenteral, intravaginal and perinatal infections with simian immunodeficiency virus in monkeys, and the safety profile gathered with TDF in humans with AIDS over the past 5 years since TDF was licensed for clin. use, it should be further pursued for the pre- and post-exposure prophylaxis of HIV infections in humans. Meanwhile, new classes of both acyclic (i.e. PMPO-DAPy, PMEO-DAPy, HPMPO-DAPy) and cyclic nucleoside phosphonates (i.e. PMDTA, PMDTT, GS9148) have been accredited with an antiviral potency and selectivity similar to those of cidofovir, adefovir and/or tenofovir.

REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 2 OF 5 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:99157 HCAPLUS <<LOGINID::20070503>>
DOCUMENT NUMBER: 142:170033
TITLE: Methods and compositions for the treatment or prevention of human immunodeficiency virus and related conditions using cyclooxygenase-2 selective inhibitors and antiviral agents
INVENTOR(S): Maziasz, Timothy
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 172 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2005026902	A1	20050203	US 2004-769485		20040130
PRIORITY APPLN. INFO.:			US 2003-443910P	P	20030131

OTHER SOURCE(S): MARPAT 142:170033
AB The present invention provides compns. and methods for the treatment of human immunodeficiency virus (HIV) infection as well as HIV associated diseases and related disorders. More particularly, the invention provides a combination therapy for the treatment of HIV infection as well as HIV associated diseases and related disorders comprising the administration to a subject of an anti-human immunodeficiency virus agent in combination with a cyclooxygenase-2 selective inhibitor or an isomer or a pharmaceutically acceptable salt, ester, or prodrug thereof.

L14 ANSWER 3 OF 5 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:857189 HCAPLUS <<LOGINID::20070503>>
DOCUMENT NUMBER: 141:325791
TITLE: Treatment and prevention of otic disorders with cyclooxygenase 2 (COX-2) inhibitors alone or in combination with otic agents

INVENTOR(S): Seibert, Karen
PATENT ASSIGNEE(S): Pharmacia Corporation, USA
SOURCE: U.S. Pat. Appl. Publ., 60 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004204471	A1	20041014	US 2004-772760	20040204
WO 2004093870	A1	20041104	WO 2004-US2990	20040204

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
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PRIORITY APPLN. INFO.: US 2003-456286P P 20030320

AB A method for preventing or treating otic disorders and otic disorder-related complications in a subject involves a monotherapy with a COX-2 inhibitor or a combination therapy with a COX-2 inhibitor and an otic agent. Also described are therapeutic compns. comprising a COX-2 inhibitor and an otic agent. Pharmaceutical compns. and kits for implementing the method are also described.

L14 ANSWER 4 OF 5 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:550871 HCAPLUS <<LOGINID::20070503>>
DOCUMENT NUMBER: 141:82300
TITLE: Methods and compositions for the treatment of herpes virus infections using cyclooxygenase-2 selective inhibitors or cyclooxygenase-2 inhibitors in combination with antiviral agents
INVENTOR(S): Maziasz, Timothy
PATENT ASSIGNEE(S): Pharmacia Corporation, USA
SOURCE: PCT Int. Appl., 155 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004056349	A2	20040708	WO 2003-US40615	20031219
WO 2004056349	A3	20040826		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
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CA 2510445	A1	20040708	CA 2003-2510445	20031219

AU 2003297397	A1	20040714	AU 2003-297397	20031219
AU 2003297397	A2	20050707		
US 2004157848	A1	20040812	US 2003-742400	20031219
EP 1572186	A2	20050914	EP 2003-813794	20031219
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2003017539	A	20051122	BR 2003-17539	20031219
CN 1726018	A	20060125	CN 2003-80106066	20031219
JP 2006512367	T	20060413	JP 2004-562315	20031219
PRIORITY APPLN. INFO.:			US 2002-435392P P	20021219
			WO 2003-US40615 W	20031219

OTHER SOURCE(S): MARPAT 141:82300

AB The present invention provides compns. and methods for the treatment of herpes virus infections. In one aspect, the invention provides a combination therapy for treating a herpes virus infection comprising the administration to a subject of an anti-herpes virus agent in combination with a cyclooxygenase-2 selective inhibitor. In another aspect, the invention provides a mono therapy for treating a herpes virus infection comprising administering a cyclooxygenase-2 selective inhibitor to a subject.

L14 ANSWER 5 OF 5 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:	1999:185447 HCAPLUS <<LOGINID::20070503>>
DOCUMENT NUMBER:	130:261355
TITLE:	Topical antiviral agents for herpes simplex virus infections
AUTHOR(S):	Hamuy, Ronnit; Berman, Brian
CORPORATE SOURCE:	Department of Dermatology and Cutaneous Surgery, University of Miami School of Medicine, Miami, FL, USA
SOURCE:	Drugs of Today (1998), 34(12), 1013-1025 CODEN: MDACAP; ISSN: 0025-7656
PUBLISHER:	Prous Science
DOCUMENT TYPE:	Journal; General Review
LANGUAGE:	English

AB A review with 53 refs. Several antiviral agents against herpes simplex virus (HSV) infection have been clin. studied. Earlier therapies include glutaraldehyde, povidone-iodine, butylated hydroxytoluene and ether. Nucleoside analogs have been tested for efficacy in HSV. Although acyclovir and adenine arabinoside have shown minimal therapeutic benefit, cidofovir has been successful in the treatment of acyclovir-resistant strains of HSV, and idoxuridine 15% in DMSO, edoxudine and penciclovir have significant clin. benefit against HSV. Interferon-α has shown synergism with other anti-HSV drugs such as caffeine, trifluorothymidine, DMSO and nonoxynol-9, and ascorbic acid shows promising effects against HSV. Using a vehicle that enhances skin penetration of a drug or further exploring combination therapy may result in efficacious treatment of HSV. Vaccination or gene therapy may also prove beneficial in future studies.

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1. A combination therapy using IL-12 and soluble IL-4 receptor on herpes simplex virus Type 1 infection in a human-SCID chimera model of thermal injury.
Katakura, Tatsushi / Kobayashi, Makiko / Fujita, Kazuhiko / Herndon, David N / Pollard, Richard B / Suzuki, Fujio, *Clinical immunology (Orlando, Fla.)*, Dec 2002
...patients, have been described as inhibitors for the type 1 T cell generation. Therefore, the antiviral effects of **combination therapy** with a type 1 T cell inducer [interleukin (IL)-12] and a type 2 T cell inhibitor [soluble IL-4 receptor (sIL-4R...
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2. Herpetic neuralgia. Use of combination therapy for pain relief in acute and chronic herpes zoster.
Bajwa, Z H / Ho, C C, *Geriatrics*, Dec 2001
...diminished libido. Management of zoster-related pain should begin as soon as possible after the onset of symptoms. **Combination therapy**--including antiviral, antidepressant, corticosteroid, opioid, and topical agents--provides the most effective...
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3. Fludarabine combination therapy for the treatment of chronic lymphocytic leukemia.
Schmitt, Barbara / Wendtner, Clemens M / Bergmann, Manuela / Busch, Raymonde / Franke, Astrid / Pasold, Rita / Schlag, Rudolf / (...) / Hallek, Michael, *Clinical lymphoma*, Jun 2002
Fludarabine combination therapies have attained an increased popularity in the treatment of chronic lymphocytic leukemia (CLL). Among them, the

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combination of fludarabine/cyclophosphamide (FC) is by far the best regimen studied. Patients receiving FC at ...

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☐ **4.** A Combination Therapy Using IL-12 and Soluble IL-4 Receptor on Herpes Simplex Virus Type 1 Infection in a Human-SCID...
Katakura, T. / Kobayashi, M. / Fujita, K. / Herndon, D.N. / Pollard, R.B. / Suzuki, F., *Clinical Immunology*, Dec 2002
...95300-3 Elsevier Science (USA) Regular Article A **Combination Therapy** Using IL-12 and Soluble IL-4 Receptor on Herpes...generation. Therefore, the antiviral effects of **combination therapy** with a type 1 T cell inducer [interleukin (IL...

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☐ **5.** Experimental herpes simplex virus encephalitis: a combination therapy of acyclovir and glucocorticoids reduces long-term magnetic resonance imaging abnormalities.
Meyding-Lamadé, Uta K / Oberlinner, Christoph / Rau, Philipp R / Seyfer, Sonja / Heiland, Sabine / Sellner, Johann / Wildemann, Brigitte T / Lamadé, Wolfram R, *Journal of neurovirology*, Feb 2003
Despite early antiviral treatment, herpes simples virus encephalitis (HSVE) still remains a life-threatening sporadic disease with high mortality and morbidity. In patients and in experimental disease, chronic progressive magnetic resonance imaging (MRI) ...

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☐ **6.** Effect of a combination therapy between IL-12 and soluble IL-4 receptor (sIL-4R) on Candida albicans and herpes simplex virus type I infections in thermally injured mice.
Kobayashi, Makiko / Takahashi, Hitoshi / Herndon, David N / Pollard, Richard B / Suzuki, Fujio, *Canadian journal of microbiology*, Oct 2002
The effectiveness of a combination using IL-12 and soluble IL-4 receptor (sIL-4R) to treat severe infections of herpes simplex virus type 1 (HSV-1) and Candida albicans in thermally injured mice was investigated. Although sIL-4R decreased burn-associated ...

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☐ **7.** Replication-competent herpes simplex virus vector G207 and cisplatin combination therapy for head and neck squamous cell carcinoma.
Chahlavi, A / Todo, T / Martuza, R L / Rabkin, S D, *Neoplasia (New York, N.Y.)*, Jun 1999
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☐ **8.** Synergistic therapy by acyclovir and A1110U for mice orofacially infected with herpes simplex viruses.
Ellis, M N / Lobe, D C / Spector, T, *Antimicrobial Agents and Chemotherapy*, Dec 2003
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☐ **9.** Combined Antiviral Effect of Interferon and Acyclovir on Herpes Simplex Virus Types 1 and 2
Stanwick, Trevor L. / Schinazi, Raymond F. / Campbell, Donald E. / Nahmias, Andre J., *Antimicrobial Agents and Chemotherapy*, Dec 2003
Acyclovir and human interferon displayed an additive to synergistic effect in reducing the number of herpes simplex viral plaque-forming units in Vero cells, suggesting a therapeutic potential for such **combination therapy**.

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☐ **10.** Topical treatment of infection with acyclovir-resistant mucocutaneous herpes simplex virus with the ribonucleotide reductase inhibitor 348U87 in combination with acyclovir.
Safrin, S / Schacker, T / Delehanty, J / Hill, E / Corey, L, *Antimicrobial Agents and Chemotherapy*, Dec 2003
...preparation of 348U87 (3%) in combination with acyclovir (5%) in an open-labelled study. Transient improvement with **combination therapy** occurred frequently; however, target lesions reepithelialized completely in only 1 of 10 patients. Termination...

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☐ **11.** Irrational prescribing in South Asia: a case of fluoroquinolone-associated phototoxicity.
Cave, William / Pandey, Prativa / Chatterjee, Santanu, *Journal of travel medicine : official publication of the International Society of Travel Medicine and the Asia Pacific Travel Health Association*, Sep 2003
...conclude that the quality of prescribing is poor, with overuse of antimicrobials and irrational use of fixed-dose **combination therapy**, particularly in the private sector.1 Prescriptions for multiple drugs are the rule rather than the exception...

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☐ **12.** Antiviral Activity of a Selective Ribonucleotide Reductase Inhibitor against Acyclovir-Resistant Herpes Simplex Virus Type 1 In Vivo
Duan, Jianmin / Liuzzi, Michel / Paris, William / Lambert, Michelle / Lawetz, Carol / Moss, Neil / Jaramillo, Jorge / (...) / Cordingley, Michael G., *Antimicrobial Agents and Chemotherapy*, Sep 2002
...BILD 1633 SE also significantly decreased the lesions caused by HSV-1 dlsptk infection (28 to 51% AUC reduction). **Combination therapy** with topical BILD 1633 SE (5%) and ACV in drinking water (5 mg/ml) produced an antiviral effect against HSV-1...

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☐ **13.** Safety of Didanosine plus Stavudine Combination Therapy in HIV-infected Subjects in a Pilot Randomized Double-blinded...
Pollard, R. / Hardy, D. / Peterson, D. / Pottage, J. / Hellmann, N. / Skovronski, J. / Reynolds, L. / (...) / McLaren, C., *Antiviral Research*, Mar 1995
143 Safety of Didamosine plus Stavudine **Combination Therapy** in HIV-infected Subjects in a Pilot Rerdomized...preliminary data suggest that didanosine+stavudine **combination therapy** can be safely administered at several dose combinations...

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☐ **14.** Enhancement of thymidine kinase-mediated killing of malignant glioma by BimS, a BH3-only cell death activator.
Yamaguchi, T / Okada, T / Takeuchi, K / Tonda, T / Ohtaki, M / Shinoda, S / Masuzawa, T / (...) / Inaba, T, *Gene therapy*, Mar 2003
...the results of clinical trials have been disappointing. To improve the performance of tk/GCV therapy, we tried **combination therapy** designed to enhance its cytotoxic effects by introducing genes that induce apoptosis of the tumor cells through...

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☐ **15.** Therapeutic effects of IL-12 combined with benzoylmesaconine, a non-toxic aconitine-hydrolysate, against herpes simplex virus type 1 infection in mice following thermal injury.
Kobayashi, Makiko / Takahashi, Hitoshi / Herndon, David N / Pollard, Richard B / Suzuki, Fujio, *Burns : journal of the International Society for Burn Injuries*, Feb 2003
...cells). In the present study, the effects of a **combination therapy** using IL-12 and BEN to treat severe HSV-1 infection...in combination. These results suggest that the **combination therapy** of IL-12 (an inducer of type 1 T cell responses...

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☐ **16.** Ribavirin derivatives with a hexitol moiety: synthesis and antiviral evaluation.
Van Aerschot, Arthur / Schepers, Guy / Busson, Roger / Rozenski,

Jef / Neyts, Johan / De Clercq, Erik / Herdewijn, Piet, *Antiviral chemistry & chemotherapy*, Jan 2003
Current standard therapy for the treatment of chronic infections with hepatitis C virus consists of **combination therapy** with (pegylated) interferon-alpha and ribavirin. 1,5-Anhydrohexitol nucleoside analogues are constrained congeners known to mimic...

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☐ **17.** Replication-selective herpes simplex virus type 1 mutant therapy of cervical cancer is enhanced by low-dose radiation.
Blank, Stephanie V / Rubin, Stephen C / Coukos, George / Amin, Kunjlata M / Albelda, Steven M / Molnar-Kimber, Katherine L, *Human gene therapy*, Mar 2002
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☐ **18.** Effect of combination therapy with adenine arabinoside (ara-A) and acyclovir (ACV) in a murine model of herpes simplex...
Antiviral Research, Jan 1988
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☐ **19.** Viral infections of the CNS with special emphasis on herpes simplex infections.
Schmutzhard, E, *Journal of neurology*, Jun 2001
...Nevertheless, if other causes for the clinical/neurological syndrome of peripheral facial palsy have been excluded, a **combination therapy** with acyclovir plus prednisone seems to be indicated in a patient with Bell's palsy.

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☐ **20.** [Herpes zoster associated encephalitis with rapid response to a combination therapy with acyclovir, prednisolone and human gamma-globulin]
Toyoda, H / Tomeoku, M / Fujioka, H / Hamada, M / Kanamaru, M, *Nippon Ronen Igakkai zasshi. Japanese journal of geriatrics*, Nov 1991

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Herpes simplex virus **thymidine kinase** (HSV-tk)/gancyclovir (GCV) therapy has the ability to...To improve the performance of tk/GCV therapy, we tried **combination therapy** designed to enhance its cytotoxic effects by introducing...

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2. Novel mutations in the thymidine kinase and DNA polymerase genes of acyclovir and foscarnet resistant herpes simplex...
Chibo, D. / Mijch, A. / Doherty, R. / Birch, C., *Journal of Clinical Virology*, Aug 2002
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...dlsptk and PAAr5, which contain mutations in the viral **thymidine kinase** gene and the polymerase gene, respectively. Following...caused by HSV-1 dlsptk infection (28 to 51% AUC reduction). **Combination therapy** with

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Murata, K. / Fujita, M. / Yamada, Y. / Higami, Y. / Shimokawa, I. / Tsukasaki, K. / Tanaka, Y. / (...) / Yoshiki, T., *Japanese Journal of Cancer Research*, May 1997
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☐ **5.** Selective radiosensitization of 9L glioma in the brain transduced with double suicide fusion gene.
Kim, J H / Kolozsvary, A / Rogulski, K / Khil, M S / Brown, S L / Freytag, S O, *The cancer journal from Scientific American*, Nov 1998
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☐ **6.** Tissue-specific expression of HSV-tk gene can induce efficient antitumor effect and protective immunity to wild-type hepatocellular carcinoma.
Kuriyama, S / Sakamoto, T / Masui, K / Nakatani, T / Tominaga, K / Kikukawa, M / Yoshikawa, M / (...) / Tsujii, T, *International journal of cancer. Journal international du cancer*, May 1997
The efficacy of expression of the herpes simplex virus **thymidine kinase** (HSV-tk) gene under the transcriptional control of the...wild-type HCC cells. Our results indicate the feasibility of **combination therapy** with the HSV-tk gene and ganciclovir for the treatment...

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☐ **7.** Enhanced Therapeutic Effect of HSV-tk+GCV Gene Therapy and Ionizing Radiation for Prostate Cancer
Chhikara, M. / Huang, H. / Vlachaki, M.T. / Zhu, X. / Teh, B. / Chiu, K.J. / Woo, S. / (...) / Oberg, K.C., *Molecular Therapy*, Apr 2001
...in lung colonization. Primary tumors that received the **combination therapy** had a marked increase in CD4 T cell infiltrate. This is...ongoing. gene therapy radiotherapy herpes simplex virus **thymidine kinase** adenoviral vector prostate cancer References 1 Dalkin...

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☐ **8.** Antiviral activity of a selective ribonucleotide reductase inhibitor against acyclovir-resistant herpes simplex virus type 1 in vivo.
Duan, J / Liuzzi, M / Paris, W / Lambert, M / Lawetz, C / Moss, N / Jaramillo, J / (...) / Cordingley, M G, *Antimicrobial agents and chemotherapy*, Jul 1998
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Atkinson, G. / Hall, S.J., *Urology*, Dec 1999
...simplex virus **thymidine kinase** gene (HSV-tk...GCV-mediated killing, **combination therapy** continued to...potential benefit of **combination therapy** in patients...simplex virus **thymidine kinase** gene (HSV-tk...by endogenous **kinases**. The triple...benefits of **combination therapy**. Material and...

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☐ **10.** Changing paradigms in dermatology: antivirals in dermatology
Lin, P. / Torres, G. / Tyring, S.K., *Clinics in Dermatology*, Sep 2003
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☐ **11.** Connexin 43-Enhanced Suicide Gene Therapy Using Herpesviral Vectors
Marconi, P. / Tamura, M. / Moriuchi, S. / Krisky, D.M. / Niranjan, A. / Goins, W.F. / Cohen, J.B. / Glorioso, J.C., *Molecular Therapy*, Jan 2000
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☐ **12.** Synergistic therapy by acyclovir and A1110U for mice orofacially infected with herpes simplex viruses.
Ellis, M N / Lobe, D C / Spector, T, *Antimicrobial agents and chemotherapy*, Oct 1989
...but one experiment, the effect of **combination therapy** was greater than that calculated...in mice. In several experiments, **combination therapy** totally eliminated all signs of...These results indicate that this **combination therapy** may provide a significant improvement...

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☐ **13.** Oncolytic viruses and cancer therapy
Norman, K.L. / Farassati, F. / Lee, P.W.K., *Cytokine and Growth Factor Reviews*, Jun 2001
...improve on efficacy include incorporation of cytotoxic genes, such as tumor necrosis factor in Ad.DF3-E1, and herpesvirus **thymidine kinase** in E1B-deleted adenovirus [36,37] . Such alterations have been shown to promote more effective and sustained tumor regression...
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☐ **14.** Enhancement of the anti-herpetic effect of trichosanthin by acyclovir and interferon
Zheng[a], Y.T. / Chan[b], W.L. / Chan[c], P. / Huang[b], H. / Tam[b], S.C., *FEBS Letters*, May 2001
...play an attractive role in **combination therapy**. In this study, the effect...particularly sensitive to TCS. **Combination therapy** using more than one anti-viral...phosphorylated by HSV-specific **thymidine kinase** [7] . It is therefore active...
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☐ **15.** Combination of benzo[a]phenothiazines with acyclovir against herpes simplex virus
Mucsi, I. / Molnar, J. / Motohashi, N., *International Journal of Antimicrobial Agents*, Jul 2001
...alone [14] , if the second drug has a different mechanism of activity. ACV selectively inhibits herpes viruses having a **thymidine kinase** (TK). The viral TK activates the drug by phosphorylation to a monophosphate and this is subsequently converted by cellular...
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Antiviral Research, Apr 2000
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Oh, K.-W. / Lee, C.-K. / Kim, Y.-S. / Eo, S.-K. / Han, S.-S., *Journal of Ethnopharmacology*, Sep 2000
...cells by phosphorylating HSV-derived **thymidine kinase**. However, the prolonged therapies...the new antiherpetic agents, and **combination therapy** with currently available drugs is...both as a potential antiherpetic

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Lobe, D C / Spector, T / Ellis, M N, *Antiviral research*, Feb 1991
Combination therapy with A1110U, an inactivator of the...mice infected with an ACV-resistant **thymidine kinase**-deficient mutant and an ACV-resistant TK-altered mutant HSV-1 isolated. **Combination therapy** was very effective in reducing lesion...
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Safrin, S / Schacker, T / Delehanty, J / Hill, E / Corey, L, *Journal of medical virology*, Jan 1993
...effects against infections in mice due to **thymidine kinase**-deficient, **thymidine kinase**-altered, and DNA polymerase mutants of HSV. We performed a pilot study of topical **combination therapy** with 348U87 (3%) and acyclovir (5%) cream...
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